

Cardiff School of Pharmacy & Pharmaceutical Sciences Research Abstracts

16th Edition 2016

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Published by STS Publishing, Redwood Building, Cardiff CF10 3NB, Wales, United Kingdom

Published June 2016

ISBN: 9780948917523

British Library Cataloguing-in-Publication Data.

A catalogue record for this book is available from the British Library.

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FOREWORD

The School of Pharmacy and Pharmaceutical Sciences, Cardiff University, is the only school of pharmacy in Wales and is one of the top schools of pharmacy in the UK. Our students graduate well-prepared and satisfied, as seen by the consistently high pass rate in the pharmacist registration examination and high ranking in the National Student Survey respectively.

In addition to supporting individual pharmacists in their initial and ongoing education and development, the School is active in research that has been independently judged to be predominantly of international standing, more than half of which is recognised as world-leading or internationally excellent and with many interdisciplinary and external collaborators. Research at the School encompasses medicinal chemistry, drug delivery and microbiology, pharmacology and physiology, and pharmacy practice and clinical pharmacy, and it impacts on healthcare and pharmaceutical sciences throughout the UK and the world. Further information on the School's research activities and degree programmes, along with contact details for academic staff can be found at <http://www.cardiff.ac.uk/phrmy>.

At the Cardiff School of Pharmacy and Pharmaceutical Sciences, the combination of these strengths allows us to successfully deliver research-led learning and teaching. All of our MPharm students undertake a significant, independent Masters level research project in the final year of the four-year degree, and present and defend their research. The high numbers of well-qualified UK, EU and international students that we attract to our postgraduate diplomas and degrees also contribute significantly to our research output.

This is the 16th year in which we have published the abstracts of our students' research. Within this publication the student is the first named author, and collaborators and supervisors follow. An alphabetical list of authors appears in the index.

Many thanks to our colleagues for their assistance in collating this book.

Rebecca Price-Davies & Justine Jenkins
June 2016

Numerical approach to investigate adhesion between orthopaedic biomaterials and staphylococcus bacteria

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Biomaterial-associated infections (BAIs) are the third most common cause of revised orthopaedic surgery.¹ Bacteria naturally favour the inert environment of biomaterials where they attach and adhere to the surface through non-specific and specific interactions. This encourages formation of a highly resistant structure known as a biofilm. Treating such infections is very difficult and often leads to implant failure resolved only by surgical removal. Consequently bacterial adhesion is recognised as a critical stage responsible for the pathogenesis of BAIs.^{2,3}

This study examines the adhesion of *S. aureus* and *S. epidermidis* on metallic and polymeric biomaterials pertinent to orthopaedics. The predefined elastic modulus and surface energy parameters of the biomaterial and bacteria were correlated with microbial adhesion through Johnson, Kendall and Roberts (JKR) multiasperity adhesion model. This approach, proposed by Prokopovich and her research group, quantifies the adhesive forces between the assumed biomaterial's rough, elastic surface and bacteria's smooth, rigid surface within a liquid medium.⁴

The results suggest an inverse relationship between surface energy and elastic modulus on bacterial adhesion, the latter showing overriding effects. *S. aureus* displayed the greatest adhesive ability to the most rigid metallic and polymeric biomaterials Co-Cr alloy and UHMWPE respectively. Surface energy seemed to potentiate the adhesive force strength and relied on the bacteria rather than biomaterial surface tension. This is explained by the ability of low surface energy bacteria to spontaneously coat and stick to higher surface energy materials resulting in stronger attractive forces. *S. epidermidis* and Ti alloy exhibited strongest adhesive forces though their surface energies are comparable. In light of this discrepancy, other surface and material factors are discussed including hydrophobicity and surface charge.

In general respects, biomaterial physical properties appear to dominate over surface parameters, placing greater importance on elastic modulus for future studies. The adhesiveness of bacteria confirms to be strain specific especially for *S. epidermidis*.

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Alcohol misuse and intervention: the development and evaluation of a computer assisted learning package

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CAL can be described as an effective and interactive method of facilitating learning and self-assessment procedures via the use of computers.¹ The aim of this study was to assess the potential use of CAL packages on the topic of alcohol misuse and its intervention, to be used as a learning aid by MPharm III students.

The CAL package was constructed using Microsoft PowerPoint and included up-to-date information regarding the management of alcohol misuse.² In order to retain student focus, aspects such as appearance, content and structure were considered.³ The role of the pharmacist was included, allowing students to relate the content to their profession.⁴ A questionnaire was designed using GoogleDocs for anonymity, employing a five-point Likert scale and some open questions to evaluate students' opinions on the appearance, content, and overall impression of the package and CAL in general.

A total of 30 questionnaires were completed (response rate=25.6%), and the frequency and mode of Likert response scores were calculated. All students felt that the package was well presented, while 96% (n=29) believed the package had covered the relevant information regarding alcohol misuse. Most students (93%, n=28) felt that the role of the pharmacist was now clear to them, with positive feedback also obtained from open questions. Fifty per cent (n=15) stated they would prefer to learn from CAL rather than conventional methods, however when asked whether they would like a lecture to be given alongside the package, 73% (n=22) indicated in the affirmative.

The package overall was well received, as students found that it was effective and relevant. Further interactive material, such as audio, video and case studies would enrich the quality of the package, and serve to gratify students using CAL. The use of CAL throughout the MPharm course could prove to be very beneficial to students, particularly in conjunction with lectures.

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Anti-cancer properties of frankincense extract

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Natural products represent a significant and important starting point in drug discovery. *Boswellia frereana* (BF) is a frankincense that is only found in Somalia, unlike other frankincense it does not contain boswellic acids. However, about 60% of the resin contains epi-lupeol, BF's active.¹ Epi-lupeol is a diastereoisomer of lupeol and effects MMP9 levels.²

The aim of this study is to investigate the *Boswellia* extract, BF4, in a broader, breast cancer specific context by assessing its anti-tumour activity in a panel of breast cancer models reflecting the major clinical subtypes. The specific project objectives were to determine whether BF4 could inhibit cancer cell growth, using MTT assays, and migration, using cell 'wounding' assays.

Our results show that the MDA231 cell line were most sensitive to BF4 and they showed a clear dose dependent inhibition of cell growth and migration. There are increased levels of MMP9 in breast cancer tissue in comparison with normal breast tissue and they are particularly abundant in the aggressive TNBC subtype.[2] Literature states that BF4 effects MMP9 levels and this could potentially explain our results.³

To conclude, BF4 dose dependently inhibits the growth of MDA231 cells in contrast to the other cell types, where the effect was only observed at the highest concentration of 80ug/ml of BF4. Our data shows that *Boswellia frereana* which contains epi-lupeol may have potent anticancer activities particularly in the TNBC subtype where there are no current targeted therapies.

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Synthesis of oroidin analogues and evaluation of their antimicrobial properties

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The marine environment is a rich source of novel bioactive compounds. Marine sponges produce secondary metabolites as a part of their natural defence mechanism to deter predators and competition from other sponge species. Oroidin, which is a marine sponge metabolite first isolated from the sponge *Agelas oroides*, has been shown to possess antibiofouling¹, antiprotozoal² and antifungal³ properties. With the emergence of antibiotic

resistance combined with the decline in the research discovery of novel antibiotics, it has become an urgent need to search for novel lead compounds with promising antibacterial properties. The linear structure of oroidin and its interesting biological properties, renders it as an ideal candidate for structure manipulation strategies. Hence, this study aims to synthesise oroidin analogues in an effort to produce compounds with antimicrobial activity.

The synthesis of the analogues involves a two-step procedure. The oroidin scaffold was prepared by reacting 2-(trichloroacetyl)pyrrole with bromine to form 4,5-dibromo derivatives. The target compounds were then formed by the coupling of the pyrrole compounds – with and without the bromine substitution – with four structurally different amines via a nucleophilic displacement reaction. The antimicrobial activities of the analogues were assayed using the agar well diffusion method against *Staphylococcus aureus*.

Of the four analogues prepared, only one displayed antimicrobial activity against *S. aureus* with a zone of inhibition of 12 mm at a concentration of 1.0 mg/mL. The active analogue had the bromopyrrole moiety whilst the other three inactive analogues were non-halogenated compounds.

The contrasting results between the active analogue and its non-brominated counterpart suggest structure activity relationships and that the dibromopyrrole group is involved in the antimicrobial activity. With improved chemical methods and further chemical optimisation of the dibromo analogue synthesis, the compounds would serve as a good foundation for a future class of novel antibiotic drugs.

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Drug release across aural implant devices for the treatment of otitis media and otitis externa

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Otitis externa (OE) and otitis media (OM) are two common inflammatory conditions affecting the outer and middle ear. 1% of patients experience OE annually and 75% of children under the age of 10 experience OM.^{1,2} Severe cases can result in the insertion of an ear wick in OE or grommet in OM.^{2,3} These interventions result in pain, increased clinical visits and significant costs for the NHS. Aural implants may however present an opportunity for the delivery of therapeutics.⁴ This study aims to determine whether candidate drugs can permeate through, or elute from biodegradable materials representing a drug eluting stent in OE and drug permeable grommet in OM.

Three biodegradable polymers and a clinically appropriate antibiotic, anaesthetic and anti-inflammatory were selected. Drug-loaded discs were submerged in PBS, whilst polymer films were placed in Franz-type diffusion cells where drugs were applied via the donor chamber. Aliquots of the sample medium were taken at designated time intervals for UV-Visible spectroscopic analysis and results were plotted as cumulative release.

Release studies found that hydrophilic drugs were released in greater quantities than hydrophobic drugs from each polymer, however therapeutic concentrations were not achieved. Permeation studies showed two of the polymers were poorly permeable to candidate drugs and the third was too brittle to be used.

Poor permeability suggests that these polymers may not be suitable for drug permeable grommets, but testing further materials and tailoring their parameters as drug eluting stents could be possible. Treating OE and OM more effectively could result in reduced clinical visits, controlled drug delivery and improved patient compliance, however controlled release is a complex process that relies upon numerous parameters. The small number of sample repeats required more samples to be tested in more standardised discs in order to make definitive conclusions.

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Study of inhaler technique of the patients of the Cardiff and Vale University Health Board

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Inhalers are the cornerstone of the treatment of respiratory disease.¹ Poor inhaler technique is well documented, however there is a lack of engagement between patients and healthcare professionals on this issue.² This study looks aims to establish the quality of patients' technique with different inhalers in the Cardiff and Vale area.

Data for the study was gathered through patient interviews as well as assessing patient inhaler technique through use of the AIMs device, an electronic monitor for measuring patient technique, and patients were provided with advice on how to improve their technique. Chi-squared analysis was carried out on the data collected to identify any statistically significant results.

The study showed that MDIs as lone devices are far less reliable when compared to DPIs, as well as when they are compared to MDIs used with a spacer device (p-value <0.0001). It also identified that current advice given to patients on how to use their inhalers has little or no effect on how they use them from day to day.

Changes in the way patients are being shown how to use their inhalers needs to change. Patient technique would benefit from physical demonstrations.² To improve patient outcomes, prescribers should aim to give ICs in the form of DPIs or MDIs with spacers. Prescription of combination IC/IB inhalers should be seriously considered as a way of increasing patient adherence to IC maintenance therapy.^{3,4}

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Investigating the role of ZIP7 phosphorylation in breast cancer

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A link has been identified between zinc release and the prolonged activation of growth factors in endocrine resistant breast cancer, the mechanism responsible is thought to be ZIP7 mediated zinc induced activation of the proliferative tyrosine kinase pathways, via inhibition of tyrosine phosphatases.^{1,2} The aggressive growth of Tamoxifen resistant breast cancer cells can be attributed to their increased expression of the ZIP7 transporter¹ which causes increased intracellular zinc. Two consecutive serine residues have been identified as phosphorylation sites of ZIP7, located at residues S275 and S276.³ This study considers ZIP7 phosphorylation at the S275/S276 sites as well as investigating the importance of each of the S275 and S276 residues individually in the phosphorylation process. Potential downstream targets of ZIP7 mediated zinc release known to be linked to growth and invasiveness were also examined (CREB and mTOR).

MCF-7 cells were transfected with a variety of ZIP7 constructs, both wild-type and mutated, to examine the role of the S275 and S276 residues. The mutants used were S275A/S276A, S275D/S276A and S275A/S276D. Transfected cells were treated with an exogenous zinc stimuli and detected by chemiluminescence, results were normalised to beta-actin by densitometry.

Our findings in the wild-type and phospho-null mutant (S275A/S276A), when probed for pAKT and pZIP7 were consistent with previously published DATA [3], confirming that residues S275 and S276 were the principle phosphorylation sites of ZIP7. Our examination of the S275 and S276 residues individually was inconclusive, with conflicting data suggesting both the residues may be required for ZIP7 mediated zinc release and that the S276 residue alone may initiate ZIP7 phosphorylation. Novel data characterising pCREB and pmTOR response to exogenous zinc stimulation was also gathered, highlighting possible pathways leading to cancer growth and survival.

Further research combined with a crystal structure of ZIP7 could lead to the development of much needed therapeutic agents to combat anti-endocrine resistant breast cancers and further our understanding of the mechanisms behind the development of resistance.

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A preliminary investigation into the impact of the WEDINOS Project

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New Psychoactive Substances (NPS), also known as 'legal highs', can be defined as 'substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat'.¹ NPS are designed to produce much the same psychoactive effect on the body as illicit drugs like ecstasy and cannabis. With reported incidence of NPS on the rise², so-called 'legal highs' should be assumed to be neither safe nor legal. WEDINOS provides a robust mechanism for the collection and analysis of NPS and unidentified substances, as well as pragmatic harm reduction advice.³ The aim of this study is to gain a preliminary insight into the impact of WEDINOS, and begin to investigate knowledge and opinions surrounding NPS use.

The investigation was conducted via one-to-one semi-structured interviews with three participant groups. This included two peer participant groups (student peers and community peers) and one criminal justice participant group. Non-probability sampling was used to recruit participants. Results were analysed qualitatively through content analysis. Further analysis took place quantitatively through the comparison of numerical charts of 'yes' or 'no' answers. Ethical approval was obtained.

Results revealed a profound lack of knowledge of the surrounding issues of NPS use. Many peer participants believed the terminology behind so-called 'legal highs' equated them to being safe and decidedly legal. All criminal justice participants reported NPS misuse as a problem in their area. A sizeable proportion of participants were not aware of the WEDINOS project, and all felt more needed to be done to raise awareness in their respective communities. Limitations identified were small sample sizes and a lack of probability sampling for quantitative analysis.

Further impact studies on a larger scale need to be conducted to gain a conclusive insight into the impact of WEDINOS. Public Health Wales intend on conducting such an impact study in the near future.

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Evaluating the suppression of DET1 and PRUNE2 genes in endocrine resistant breast cancer

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Most breast cancers express oestrogen receptor (ER+). These can be subdivided into luminal A (HER2-) and luminal B (HER2+) disease. For ER+ patients, endocrine therapy is the main treatment, however resistance is a significant problem.¹ To discover mechanisms of resistance, an *in vitro* panel was developed from endocrine responsive parental cells. This panel mimics resistance to prolonged endocrine treatment in luminal A (MCF7,T47D) and luminal B disease (BT474,MDA361).² Preliminary Affymetrix results found suppression of genes PRUNE2 and DET1 in BT474-derived resistant models. The main aim of this project was to use the

model panel and bioinformatics to further explore whether suppression of PRUNE2 or DET1 might contribute in driving endocrine resistance.

PCR was used to verify the Affymetrix profile in BT474-derived cells and determine any PRUNE2 or DET1 mRNA suppression in the panel and whether it was related to ER profile. Densitometry semi-quantified expression. KM plotter examined prognostic value of the genes using publically-available datasets. Gene ontology was interrogated using the online resources PubMed and GeneCards to see whether these genes were inhibitory in cancer.

The Affymetrix profile was broadly confirmed and there was suppression of DET1 and PRUNE2 in many luminal B derived models. PRUNE2 was suppressed in some MCF7-derived but not T47D-derived models. No marked association with ER profile was seen. KM plotter found for both PRUNE2 and DET1, lower expression associated with shorter time to tamoxifen relapse. Lower hazard ratios were seen in luminal B cohorts supporting the model findings that DET1 and PRUNE2 suppression was probably more involved in luminal B-derived resistance. Ontology indicated both genes had tumour-suppressive properties.^{3,4}

The project findings indicate suppression of PRUNE2 and DET1 could be involved in driving luminal B-derived endocrine resistance in breast cancer. Further research could potentially result in new therapeutics to combat such disease.

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Evaluation of inhaler technique in patients of the Cardiff and Vale University Health Board

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The efficacy of an inhaler is greatly dependent on a patient's ability to use their device.¹ Many patients have poor inhaler technique² and therefore do not receive a sufficient dose of medication. This could lead to their respiratory condition becoming un-controlled, and an overall decreased quality of life.³ Training patients correctly is therefore of paramount importance.

The aim of this study was to assess patient inhaler technique. This was done using the Vitalograph Aerosol Inhalation Monitor (AIM), a device that estimates drug deposition at different levels of the lung. Low deposition in the deep lung correlates with inadequate technique. Patients were asked a short questionnaire to gather demographic and inhaler usage data. Excel was used to sub-group the data, which was then analysed using Chi-Squared to identify whether the differences in results were of statistical significance ($P < 0.05$).

MDI +Spacer users had significantly better technique than DPI users, who in turn were statistically better than patients who used a MDI (without spacer). Poor co-ordination, inspiring too slowly/quickly or holding breath for less than 5 seconds resulted in a "fail". Overall, 82% of MDI users failed the test compared to 17% who used a DPI and only 9% who used a Spacer with their MDI. Being shown how to use an inhaler had no statistically significant impact on assessment result. This study found that over one third of patients had no knowledge of how taking corticosteroid inhalers helps their condition.

Overall, patients of the Cardiff and Vale University Health Board have inadequate inhaler technique. Improvements in patient education and training provided by healthcare professionals need to be made.

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Investigating what the public know about reporting Adverse Drug Reactions

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An Adverse Drug Reaction (ADR) is an unwanted or harmful side effect that can occur after the administration of any medicine.¹ The aim of this research project was to design and pilot a questionnaire for the Yellow Card Centre Wales, in order to gather information surrounding the public's views and experiences reporting ADRs.

A postal questionnaire was chosen as the most appropriate method of collecting the data.² ADRs are rare medical events, therefore purposive sampling was chosen to target those most at risk of having an ADR. Literature showed that those that were elderly, living with a limiting long term illness and with a lower socio economic status were most likely to experience an ADR. Census data was then used to determine electoral wards in Cardiff with the highest and lowest density of individuals in these three categories. After ethical consideration, the questionnaire and a cover letter were sent to 400 members of the public.

There was a 14% response rate (n=55) with an even distribution of gender and those with / without a limiting long term illness. The mean age of respondents was 50 (SD 19.03). Thirty-one respondents had heard of the term 'Adverse Drug Reaction' and twenty-eight had experienced an ADR themselves. Of the 55 that responded to the questionnaire, only nine respondents had heard of the YCS and just two had reported an ADR through the YCS. Preferred methods of reporting were online, by post and by smartphone app. The most popular methods of learning more about the YCS were online and through social media.

The results are in line with studies previously carried out that suggest an increase in the awareness of Adverse Drug Reactions is needed to improve pharmacovigilance.³

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Molecular modelling studies on methyltransferase enzymes as a novel drug target to treat schistosomiasis

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Schistosomiasis is an infectious parasitic disease caused by the trematode fluke worm (Genus schistosoma). Usually found in fresh water like rivers and lakes, it burrows into exposed skin, the fluke matures and the females release eggs, most are excreted with some getting lodged into the hosts tissues giving rise to the clinical symptoms associated.¹ Schistosomiasis is thought to affect around 243 million people annually mostly in tropical and subtropical regions.^{2,3}

Here we try to target Methyltransferases (O-Methyltransferase and N-Methyltransferase) as novel drug targets to treat Schistosomiasis. We aligned the schistosoma fasta sequences to crystal structures of the same enzyme of different organisms, doing so we were able to create homology models of both. Using the homology models, we used docking programs consensus scoring and visual inspection to screen potential inhibitors in the active site(s) we decided to target.

For the O-Methyltransferase for both the cofactor and peptide active site, using the docking programs and consensus scoring we managed to reduce the number of potential inhibitors to 1355 and 1558 compounds respectively. Further visual inspection we identified the top 40 potential inhibitors for both. For the N-Methyltransferase only targeting the 'arm' portion of the dimer we reduced the number of inhibitors to 48,821 using HTVS, and then conducting negative screening we managed to exclude 16,390 compounds

The 40 inhibitors selected for both O-Methyltransferase active sites show a lot of promise, although selectivity may be a potential issue in the future. These will now be purchased and tested further in Aberystwyth University in the hope of identifying a lead compound. There needs to be a lot more work conducted on the N-Methyltransferase but selectivity seems promising with the high results seen from the negative screening and the differences between the target area ('arm') of the Schistosoma and Human dimer.

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Topical delivery of Rho-kinase inhibitor Y-27632 to the cornea via mucoadhesive film

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Dual cryoprobe/ROCK inhibitor treatment¹ was reported to have clinical benefit for Fuch's Dystrophy, a common hereditary corneal disease. However, prior results obtained with ROCK inhibitor Y-27632 eye drops were considered sub-optimal due to run off and drainage.² The aim of this study was therefore to test in vitro the plausibility of delivering Y-27632 to the cornea using an alternative delivery system, namely thin polymeric films to be applied directly onto the eye surface.

Thin films were prepared incorporating Y-27632 using polymers that provide mucoadhesion³, and diffusional release was determined into PBS, followed by HPLC analysis. Topical ocular delivery from the applied film was modeled using freshly excised porcine eyeballs, of which half had undergone transcorneal freezing treatment using the cryoprobe device⁴. Eye drops of equivalent concentration to the film were formulated in PBS and applied onto the porcine eyeballs along as control. After 24 hours the formulations were removed and the corneas extracted, prior to HPLC analysis.

Drug-loaded thin polymeric films, with high clarity and pliability were readily produced. ROCK inhibitor Y-27632 was weakly retained within the film, with release attaining equilibrium after 1 hour. This in turn, facilitated its rapid ocular delivery - approximately three times greater Y-27632 penetration was observed from the thin film ($p < 0.01$) compared to equivalent eye drops into cryoprobe-treated corneas.

Findings from this study support the further development of cryoprobe/ROCK inhibitor delivery from thin mucoadhesive films as a combination therapy for Fuch's Dystrophy. The results also generally support the potential development of thin mucoadhesive film as an alternative to eye drops application, by incorporating drugs targeting other conditions. The approach is however only appropriate for severe conditions that would otherwise require invasive surgery.

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Characterising nigral grafts developed in the presence of L-dopa and/or GLP-1 agonists in Parkinson's disease

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Parkinson's Disease (PD) is a chronic neurodegenerative disease, leading to reduced dopamine levels in the brain as a result of nigro-striatal degeneration. A potential treatment for PD involves transplantation of fetal ventral mesencephalon tissue into the brain to increase striatal dopamine levels.¹ Studies of this treatment have been carried out in both animals and humans, with varied results.^{2,3} GLP-1 agonists are currently being investigated for their neuro-protective effect on dopaminergic neurons. The aim of this study was to establish if GLP-1 agonists and/or L-dopa promote a neuro-protective effect on dopaminergic cells transplanted into the brain to manage the symptoms of PD.

A model of PD was simulated in rats via a unilateral 6-OHDA lesion in the nigrostriatal pathway. There were seven treatment groups undergoing the transplantation procedure. Relevant groups were treated with GLP-1 agonist and/or L-dopa, before the brains were sacrificed and analysed using immunohistochemistry techniques. Cell populations were collected using the microscope and analysed using two-way ANOVA.

There were no significant differences in the percentages of nigral dopaminergic neurons lost due to the lesion, serotonin or dopaminergic neurons in the graft, proportion of dopaminergic neurons which are the A9 subtype or inflammatory microglia in the graft and in the striatum between treatment groups. There was a significant difference in the percentage of dopaminergic neurons lost in the ventral tegmental area (VTA) between saline and liraglutide (with L-dopa) ($P=0.0361$). Rat weight was unaffected by the treatments.

To conclude, the results have suggested that GLP-1 agonists do not promote a neuro-protective effect or influence the survival of grafted dopaminergic neurons. Further work is needed to see if GLP-1 agonists promote a neuro-protective effect on other dopaminergic cell sources. However, I believe that cell transplantation show promise for the future treatment of PD, if treated early enough.

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Adhesive ability of *S. aureus* and *E. coli* to catheter materials: influence of the materials and surface properties on surface energy parameters

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The first emergence of urinary catheter was dated back in the year of 1752 invented by a politician named Benjamin Franklin. Ever since the introduction of urinary catheter, patients who exposed to the use of it have risen to at least 5 million in 2015. Today, urologists still insist on absolute disinfection to prevent microorganisms from infecting the urinary tract, as 80% of nosocomial urinary tract infections are related to urethral catheterization.¹ The bacteria that are responsible for CAUTI are mostly from *E. coli* and *S. aureus*.

The first emergence of urinary catheter was dated back in the year of 1752 invented by a politician named Benjamin Franklin. Ever since the introduction of urinary catheter, patients who exposed to the use of it have risen to at least 5 million in 2015.¹ Today, urologists still insist on absolute disinfection to prevent microorganisms from infecting the urinary tract, as 80% of nosocomial urinary tract infections are related to urethral catheterization.² The bacteria that are responsible for CAUTI are mostly from *E. coli* and *S. aureus*. From the results obtained, the hypothesise that surface of silicone has the highest adhesive force (500uN and 1000uN) towards bacteria *S. aureus* and *E. coli* are truthful.

PTFE (Teflon) is the best material available to make catheters with regard to the low adhesive force (55uN) produced between surface and bacteria *S. aureus* and *E. coli*.

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Skin permeation and penetration studies of metals using laser ablation ion coupled plasma mass spectrometry (LA-ICP-MS)

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Metal localisation in skin was relatively poorly studied, where previous methods include laser induced-breakdown spectroscopy (LIBS), electron microscopy combined with energy dispersive x-ray analysis and inductively coupled plasma mass spectrometry (ICP-MS). Laser ablation ion coupled plasma mass spectrometry (LA-ICP-MS) is a relatively new technique in biological samples analysis, its main advantages including bioimaging and higher sensitivity compared to other techniques.¹ The aim of this novel study was to quantitate the localisation of manganese and titanium in excised porcine skin following dosing with potassium permanganate wash, commercial sunscreen and lipscreen. The importance of LA-ICP-MS in toxicological

assessment in humans and animals was highlighted by detecting the levels of manganese (Mn) and titanium (Ti) in skin, two common metals used in cosmetics and medical treatment.^{2,3}

The epidermis samples were heat separated from porcine ears and treated separately with potassium permanganate wash and commercial sunscreens. By calibrating samples with modified ballistic gels containing known concentrations of metals, the manganese and titanium levels in skin were quantified by doing depth profile analysis. The average molarity and average weight of the metals were then determined.

The results obtained were semi-quantitative due to the set of standards being non-matrix matched, though a clear measure of metal concentrations can be used for toxicological and safety studies of cosmetics and topical medications. Some variations existed in the results, which represented the skin's variability and potential selective accumulations in pores and follicles.

This novel study demonstrated LA-ICP-MS as a promising method for depth profile analysis of metals in skin, with further studies required using matrix-matched standards. LA-ICP-MS could potentially be used for skin permeation and penetration studies involving new topical drugs containing metals or health and safety regulatory studies.

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Involvement of oestrogen receptor signalling in Alzheimer's disease in women

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Alzheimer's Disease (AD) is a progressive neurodegenerative disease disproportionately affecting women. Oestrogen is neuroprotective¹, it is hypothesised² post-menopause there will be an increased incidence of AD in women due to altered levels of oestrogen or oestrogen receptors (ER). GSK3 is a kinase implicated in AD due to its role in the phosphorylation of tau.³ ERs are involved with activation of GSK3 β and therefore progression of AD.⁴ The aim of this project was to determine the relationship between expression of ERs and disease progression in male and female samples.

Brain samples from male and female, AD and control donors were analysed by Western blotting to determine the amount of protein present. Samples were probed for ER α , ER β , GSK3 α , GSK3 β , APP, phosphorylated tau and total tau. Results were compared between gender and disease status.

Expression of APP was similar amongst gender and disease progression as shown previously. ER β expression was significantly higher in female AD compared to female control and male AD samples; expression was also higher in male control compared to male AD samples. ER α expression was significantly higher in female AD compared to female control samples. The expression of GSK3 β was only significantly different between male and female control samples. Higher expression of phosphorylated tau in AD samples compared to none in control samples confirmed disease staging.

This research suggests there is higher expression of ERs in women with AD. GSK3 action has been linked to oestrogen but from the results GSK3 and ER expression has been shown to be independent of one another, this may be due to the need to measure active GSK3. The progression of AD may trigger an increased synthesis of ERs allowing oestrogen to exert its neuroprotective role. The decrease in oestrogen or ERs post-menopause may predispose women to a higher risk of AD.

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Does targeted e-learning allow community pharmacy to support affected populations during a scarlet fever outbreak?

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Pharmacies are now recognised as key healthcare system entry points, as they are ideally located within the community¹, leading to an expansion in pharmacy professionals' roles in public health over recent years.^{2,3} The WCPPE have been working alongside Public Health Wales to develop e-learning resources, to better prepare pharmacy professionals to deal with communicable disease outbreaks within the community. Following an outbreak of scarlet fever in March 2015, an email prompt was sent to pharmacy professionals, living or working in areas where outbreaks occurred, to complete the related e-learning module.⁴ This study was designed to explore participants' identified changes in their knowledge and confidence in providing public health related messages on this communicable disease during the outbreak, following completion of the e-learning package. A secondary aim was to investigate whether the use of a prompting system encourages participation in e-learning.

A short structured questionnaire was sent to all pharmacy professionals who had completed the WCPPE scarlet fever e-learning package, from March 2015 onwards (n: 188). Data from the responses was collated and analysed, both thematically and via unpaired t-tests using GraphPad Prism.

A response rate of 55% was achieved (n: 104). On completion of this e-learning module, the majority of pharmacy professionals (~91%) perceived that they had sufficient knowledge and confidence to support affected populations during the outbreak. With participants (84%) successfully applying this learning in practice, for purposes such as patient counselling and education of other healthcare professionals. Data collected suggested lack of prompting would lead to non-participation of professionals (73%). Requirement for access to additional resources summarising key information to maintain new found knowledge was also expressed.

Results demonstrated that prompting to complete e-learning resources increases course uptake. Completion of communicable disease specific e-learning increases these professionals' ability to support affected populations during a scarlet fever outbreak.

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Evaluating VGLL1 in breast cancer

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VGLL1 is a co-activator for TEA domain (TEAD) transcription factors that can drive tumour proliferation.¹ Preliminary microarrays suggested VGLL1 mRNA is induced in Luminal A-derived endocrine resistant breast cancer cells that have lost oestrogen receptor (ER). This project aimed to further investigate VGLL1 in endocrine resistant models and to extend the research to protein studies including in archived clinical sections.

The Luminal A (MCF-7, T47D) and Luminal B-derived models (BT474, MDA361) used comprised an endocrine responsive control and resistance to Tamoxifen (TamR), Faslodex (FasR) or oestrogen deprivation (E₂DR). RT-PCR profiled VGLL1 expression in relation to ER loss. To detect VGLL1 protein, immunocytochemical techniques were optimised in paraformaldehyde-fixed cells and long-term stored formalin-fixed, paraffin-embedded (FFPE) breast cancer sections based on a previous assay.² The optimised clinical assay was applied to stored sections from 13 breast cancers versus ER status.

VGLL1 mRNA induction was seen in MCF-7-derived resistant TamR and FasR models and in all endocrine resistant T47D-derived models, broadly-associating with ER loss in Luminal A-derived models. VGLL1 was not induced in Luminal B-derived models. VGLL1 protein was predominantly nuclear and increases associated with ER loss in T47D-derived resistant cells. An assay for detection of VGLL1 in archived FFPE breast cancer sections was successfully-developed using pressure cooker antigen-retrieval that was able to detect an inverse relationship between nuclear VGLL1 and ER positivity.

The relationship between ER loss and VGLL1 in Luminal A-derived endocrine resistant models suggests VGLL1 might play some part in the 20% of endocrine-treated patients who become ER- at relapse.³ This finding is important because biomarkers and targets are needed for endocrine resistance. VGLL1's nuclear localisation corresponds with its reported coactivator function in the Hippo pathway.^{2,4} The assay developed is sensitive enough for future VGLL1 study using valuable stored endocrine resistant clinical breast cancer samples.

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Investigating pharmacy involvement in preparation of local infiltration analgesia in total knee arthroplasty

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Total knee arthroplasty (TKA) is a common orthopaedic procedure which is currently associated with excruciating post operative pain¹. Local infiltration analgesia (LIA) is a relatively new method designed to combat this pain². This minimally invasive technique is part of the enhanced recovery after surgery (ERAS) approach to surgery where patients have more rapid mobilisation resulting in earlier discharge and decreased NHS costs³. Currently, there is no gold standard LIA formulation and this is putting patients at risk of serious harm from drug/calculation errors, contamination and unknown product stability⁴. The aim of the study was ultimately to determine if a safe and clinically appropriate LIA formulation could be developed for use following TKA.

Service evaluation and ethical approval were obtained, allowing a literature search to be carried out to investigate current evidence based practice. SurveyMonkey™ was used to establish the current LIA formulations and procedures used in five Welsh Hospitals providing LIA. The survey was accessed online via a weblink and comprised seventeen questions of varying format. This method reached the relevant professional target audience using quota, purposive and snowballing techniques.

A response rate of 60% was achieved. The survey met our objective in understanding what LIA formulations and procedures are used in Wales. These results mirror the literature: there is variance in local practice proving that the LIA technique is not standardised. The development of the optimal 'LIA-cocktail' requires further research to address both content and dosing of constituent parts.

In conclusion, there is an unmet clinical need to standardise best practice and to provide a ready to use standardised LIA formulation. This study aimed to address this unmet clinical need. A gold standard LIA formulation as part of a standardised analgesic regimen for this patient group would enhance patient safety.

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The public's opinion on community pharmacists having access to hospital discharge information

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The CQC published a report showing that up to 87% of patients discharged from hospital, had discrepancies with their medication.¹ Community pharmacists can potentially improve the safety of discharge medication by offering a timely review with patients. However, currently pharmacists only receive a brief discharge summary of medication changes, making it difficult to fully assess a patient and make decisions about medication suitability. These review services would be improved if pharmacists could gain the detailed discharge advice letters (DALs), given to general practitioners. Therefore the aim of this study was to quantify the opinions of the public of Wales on community pharmacists having access to patients' hospital discharge advice letters

A mailed questionnaire was used to collect such data from the public in Wales. The questionnaire, cover letter and information sheet were designed by a previous Cardiff University student.² A multi-stage sampling process was used; sending 446 questionnaire (and prepaid return envelopes) to Merthyr Tydfil and 888 to Swansea. Two weeks were allowed for data collection and on return, results were entered into an SPSS database. Descriptive frequencies were run and Chi squared tests performed.

Response rates of 13% for Merthyr Tydfil and 5% for Swansea were achieved. Demographic data showed that most respondents were aged 50+. Results showed that around 50% of respondents agreed that community pharmacists should have access to all types of hospital discharge information. Respondents believed that consent is an important aspect of information transfer. However, limited information was drawn on method of transfer, although respondents tended towards electronic transfer. It was also found that respondents worried about data security within the community pharmacy and that there was a lack of knowledge surrounding the role of the pharmacist.

More research is needed before full conclusions can be drawn, owing to low response rates. However, this study can give us an indication of the public's views on the topic. Public awareness of the role of the pharmacist and data handling within pharmacy could help address some of the issues found in this study. Also, considering the views of the public in regards to consent and information transfer, could help the policy change be viewed more positively.

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Evaluating patients' inhaler technique in Cardiff and Vale University Health Board

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Inhaled drugs form the first line administration route in the management of asthma and COPD. Inhalers provide advantages over oral administration by delivering drugs directly to the target site and having a quick onset of action.¹ However, incorrect technique can cause reduced delivery of drugs to the lungs, leading to poor disease control. Previous observational studies have shown that inhaler technique is generally poor in the patient population.^{2,3} The aim of this study was to evaluate possible factors affecting inhaler technique in the population of Cardiff and Vale University Health Board.

Participants using inhalers for either COPD or asthma were recruited and information was gathered about them and their inhalers. Their inhaler technique was then assessed using a Vitalograph Aerosol Inhalation Monitor device which quantitatively estimated drug deposition in the lung.⁴ The data was evaluated using Excel software and analysed for any significance in affecting inhaler technique performance by using chi-squared tests. $P < 0.05$ was taken as being significant.

The type of device used had a significant effect on inhaler technique ($P < 0.0001$). The best performance was seen using metered dose inhalers (MDI) used alongside a spacer with only 9% scoring an overall 'fail'

compared to MDIs, with 83% scoring an overall 'fail'. Of the participants using dry powder inhalers (DPI), 50% scored in the sub-optimal range.

When prescribers choose an inhaler device for a patient, they should consider whether the inhaler is to be used therapeutically or prophylactically and is appropriate for the patient's inspiratory effort. The patients' peak inhalation flow should be measured before prescribing DPIs as these require sufficient inspiratory effort to work. Spacers should be prescribed alongside MDIs intended for prophylactic use and regular assessments of inhaler techniques should be performed to ensure a correct inhaler technique is used and maintained.

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The Isolation of bacteriophages capable of infecting *Bacillus cereus* group organisms and *Clostridium difficile*

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Bacteriophages have been an interesting research target since the early 20th century.¹ Their ability to infect and kill specific bacteria has been used to treat infections and conditions such as pneumonia, skin ulcers and burns.^{2,3} Bacteriophages may prove useful to combat the threat of antibiotic-resistant pathogens and agents of bioterrorism. *Bacillus anthracis* is the causative agent of Anthrax, while *Clostridium difficile* associated disease can cause colitis and diarrhoea. Both diseases are potentially fatal, so investigating novel treatments and decontamination agents is of interest. This study is based on previous observations in the laboratory and sought to determine the ability of specific bacteriophages to infect both *Bacillus cereus* group organisms and *C. difficile*. The activity of these bacteriophages was also investigated across a range of temperatures.

Over the course of 7 weeks, the activity of 5 bacteriophages (RW, AB1, 3B6, γ and LC1H911) was investigated against isolates of *B. thuringiensis* CRY, non-pathogenic *B. anthracis* SdT-12 and *C. difficile* (strains 12727 & R20291). Bacteria were cultured, bacteriophages were propagated and various phage plaque assays were conducted.

RW, AB1, γ and LC1H911 phages displayed lytic activity against *B. anthracis* SdT-12 at 37°C while only LC1H911 displayed activity at 25°C and 16°C. No lytic activity was seen for any of the phages against *B. thuringiensis* CRY. When tested against *C. difficile* LC1H911 and γ showed no lytic activity. RW and AB1 phages were not tested due to time constraints. The 3B6 phage displayed no lytic activity against any of the test bacteria, therefore we cannot confirm or refute the earlier observations of activity against *C. difficile*.

In conclusion, no single bacteriophage displayed lytic activity against all of the test bacteria. The fact that the LC1H911 phage was able to lyse *B. anthracis* SdT-12 at 25° and 16°C suggests that it has potential to be developed as an environmental decontaminant against *B. anthracis*.

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Exploring pharmacists views on the integration and use of eDAL within the community pharmacy setting

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A discharge medicine review (DMR) is a service offered in Wales, to patients recently discharged from hospital.¹ The service allows community pharmacists (CPs) to check patients' medicines for discrepancies upon discharge.² A challenging aspect for CPs is to identify patients who have been discharged from hospital as a discharge advice letter (DAL) is not received directly from the hospital, and CPs rely on patients to bring a copy of their DAL to the pharmacy.¹ Electronic DALs (eDALs) sent to CPs and an online DMR form have been piloted in community pharmacies in Betsi Cadwaladar, Cardiff and Vale and Cwm Taff Health Boards; this should enable pharmacists to complete DMRs in a timely manner.³ CPs can access these through a secure online portal, the Choose Pharmacy application.¹ The aim of the study was to evaluate pharmacists' views on the feasibility and usefulness of the pilot of the eDAL and the online DMR form.

Semi-structured interviews were conducted to obtain qualitative data. Purposive and convenience sampling were used to recruit pharmacists. The interviews were conducted face to face, audio recorded and transcribed *verbatim*. The data was analysed using thematic analysis. Ethics approval was obtained.

The feedback provided by CPs regarding the usefulness of eDAL was positive. CPs felt it improved communication between hospital and the pharmacy setting. Many expressed disappointment in poor uptake of the eDAL within hospitals. The quality of the eDAL was reported as good and as helpful to pharmacists when completing DMRs, due to its easy to read format; handwriting does not need to be interpreted. Several aspects of the application proved time saving; automatic input of the information from the eDAL onto the DMR form and reimbursement through the application. Some barriers to initial implementation were raised and include technical issues.

The use of eDAL within community pharmacy is welcomed and is feasible. Suggestions have been made on how to improve issues with the current application.

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Computer-aided design and synthesis of novel c-FLIP inhibitors

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Breast cancer stem cells (bCSCs) facilitate relapse of disease and lead to formation of distant metastases, which is the primary cause of mortality in breast cancer patients. Due to heterogeneity of bCSCs there are resistance to existing treatments.¹ Tumour Necrosis Factor-Related Apoptosis Inducing Ligand (TRAIL) is a protein belonging to the TNF family of ligands, is able to induce apoptosis in tumour cells; without affecting normal cells, thus it represents an attractive anti-cancer agent.² In breast cancer, however, different cell lines are resistant to TRAIL, especially bCSCs.¹ Cellular Flice-Like Inhibitory Protein (c-FLIP) plays an important role in TRAIL-resistance, because of its ability to interfere with the TRAIL pathway, therefore preventing the TRAIL induced apoptosis.² Small inhibitors for c-FLIP has not been researched due its high similarity to caspase-8, which is a crucial protein for DISC formation in apoptotic pathway.³ However, in a previous study, the homology model of c-FLIP and caspase-8 has been constructed and using a structure-based virtual screening of commercially available compounds, one selective lead c-FLIP inhibitor at micromolar concentrations has been identified.⁴ Building from the structure of this lead compound, we have designed and synthesised 13 new derivatives.

Before synthesis, all the newly designed compounds were analysed with molecular docking studies, with the aim to evaluate their predicted binding mode within the pocket of c-FLIP and non-selectivity to caspase-8. All 13 derivatives were successfully synthesised, however some synthetic pathways require optimisation to maximise yields. These synthesised compounds will be tested on breast cancer cell lines in future studies to evaluate their activity.

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Styk1 and mTOR pathway interplay in breast cancer

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While endocrine therapy has revolutionised treatment of oestrogen receptor positive (ER+) breast cancer, many patients relapse with acquired resistance.¹ The mechanisms of resistance are poorly-understood, but 'cross-talk' between ER and the mTOR pathway is implicated.² Recently an inhibitor of the mTOR pathway, Everolimus, has been clinically-evaluated. However, many patients fail to benefit² so further pathway understanding and thereby biomarkers for Everolimus responsiveness remain needed. Research in Cardiff has found that an endocrine resistant cell line (FASR) that is highly-sensitive to Everolimus also has an increase in novel kinase, STYK1. STYK1 interplay with mTOR signalling underpins Everolimus-sensitive growth in FASR. The research question was whether there is also any evidence for a relationship between STYK1 and mTOR signalling in clinical breast cancer.

An immunohistochemical assay was optimised using pH8 pressure cooker-microwave antigen retrieval to detect mTOR signalling in breast cancer sections, monitoring phosphorylation of ribosomal protein S6 (P-RPS6). This was applied to a clinical primary breast cancer series (n=93) pre-stained for STYK1, using H-scoring to analyse staining. Statistical testing examined relationship between P-RPS6, STYK1 and further parameters available for the series.

A significant correlation (P=0.047) was found between STYK1 and cytoplasmic P-RPS6. Further significant association in the all patient group, between P-RPS6, ER-beta (P=0.036) and slight association with IGFR (P=0.052) were discovered. Such associations were also seen in ER+ tumours (p=0.044, p=0.001, and p=0.016 respectively).

These findings support a novel interplay between STYK1 and mTOR signalling activity in breast cancer. ER beta, which may regulate STYK1 expression³, and IGFR may also be involved in this cross-talk between STYK1 and the mTOR pathway. Further work is needed to explore this mechanism and to examine its prevalence in endocrine resistant disease and any relation to Everolimus outcome in further patient sample series, which will help clarify biomarker potential.

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Development of a novel natural product based germinant and biocidal mixture to enhance the decontamination of bacterial spores

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Bacillus anthracis is the pathogen responsible for anthrax and is found in many areas around the world.¹ It belongs to a group of bacteria which can form chemically resistant spores making them difficult to eliminate with traditional biocides. *Bacillus thuringiensis* is a closely related, non-pathogenic bacteria also capable of forming spores, and is often used as a surrogate for *B. anthracis*. Natural products are capable of a wide variety of effects.² Some like EGCG³ and Xanthohumol⁴ are of particular interest. Selected natural products were screened for their ability to potentiate spore germination.

The effect on germination of a range of amino acids and natural products was determined using a high-throughput plate reader screening assay and a low-throughput manual count method. An Infinite Pro® 200 plate reader was used to measure the change in absorbance of *B. thuringiensis* spores exposed to natural products and germinants. A reduction of optical density in these samples indicate germination of bacterial spores. A drop count approach was also employed to determine the effect of various compounds on the viability and germination of the *B. thuringiensis* spores.

While both approaches generated results, the degree of variation and the limited number of repeats meant that it was not always possible to draw firm conclusions. On those occasions when a full data set was obtained, the test compounds failed to stimulate spore germination in excess of that seen for the Alanine (500mmol) and Inosine (25mmol) positive control.

Due to the variation obtained in the results, and the low number of repeats, it was not possible to draw any decisive conclusions about the natural products examined in this study. While the failure of the majority of compounds to exceed the values of the positive control suggest a lack of relative activity, further studies are required to determine if this is indeed the case.

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Design and synthesis of CYP121 inhibitors as potential tuberculosis therapeutics

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Tuberculosis (TB) is “a leading cause of death worldwide”.¹ There are many challenges associated with current antibiotic therapy.² An important and unexpected link has become apparent between *Mycobacterium tuberculosis* (*Mtb*), cytochrome P450 (CYP) and possible drug targeting. CYP121 is an exclusive haemoprotein essential for *Mtb* viability.³ The only known high-affinity ligands of CYP121 are azole-antifungals and these associate with a distal water molecule to bind to the haem of the CYP121.⁴ This research aims to design and synthesise CYP121 inhibitors targeting CYP121 and showing *Mtb* activity.

Molecular Operating Environment (MOE) software allowed a database of molecules to be docked in the active site to visualise binding interactions to see whether compounds had poses that exploited the haem. Triazole and imidazole derived products aim to mimic the azole-binding mode and exploit indirect binding with a distal water molecule. Amide-coupled pyridine and imidazole products aim to extend nitrogen nearer the haem to explore whether direct binding is beneficial. Purity was analysed using TLC, melting point, ¹H-NMR and ¹³C-NMR where appropriate.

MOE suggested that all novel CYP121 inhibitors exhibited binding poses that exploited the haem. The triazole product was synthesised and sent for microanalysis and biological testing. The amide-coupled imidazole product was synthesised but not in sufficient quantity for screening. ¹H-NMR showed that the synthesis of the imidazole product was unsuccessful. The amide-coupled pyridine was not attempted due to time constraints. The synthetic pathways for all products are yet to be optimised. Microanalysis confirmed that the triazole product was successfully synthesised and biological testing data is pending. Further work is needed to optimise the synthetic pathways and screen all four potential CYP121 inhibitors.

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How can WCPPE best deliver live CPD events for the pharmacy workforce within a rural location?

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Due to the lack of healthcare professionals in rural areas, pharmacists are required to play a multidisciplinary role in the community and this requires appropriate Continuing Professional Development (CPD) training.^{1,2} Over the spring and summer of 2014, the lowest number of pharmacy professionals that attended a live CPD event in Powys was 3 and the highest was 5.³ The main aim was to find out why attendance of live CPD events in Powys is so low. This information will then be used to construct an informed questionnaire which can be distributed to a greater pharmacy population across Powys and provide quantitative feedback for review. Ethical approval was sought from the Cardiff School of Pharmacy and Pharmaceutical Sciences ethics panel. Then two focus groups were undertaken to try to understand the reasoning behind the low attendances at

events. Focus group structures were decided based on literature research. The topic guide for the focus groups contained three main open questions. Closed questions were also used as prompts. The focus group dialogues were captured, transcribed and then analysed for key themes. The key themes from both focus groups were compared and were used to construct an informed draft questionnaire.

From the two focus groups eight key themes emerged. They were: location; learning facilitators; communication; IT; timings; learning and events information; frequency; use of expert speakers.

Based on the information from the focus groups, comparisons with other professions and different organisations in other countries it is clear that Wales Centre for Pharmacy Professional Education (WCPPE) needs to make changes to its current programme in order to improve delivery and attendance at live CPD events. Once the questionnaire has been sent out, collected and analysed it will give WCPPE a better idea of what their members want from events.

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Investigations into the effects of glucose on intravenous lipid emulsion stability

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Intralipid® (INT), a soybean lipid emulsion, has been used for many years due its high safety profile. SMOFlipid® (SMOF) is a new product, containing fish oils which are clinically beneficial due to the increased ω -3 and ω -6 fatty acid composition that can prevent inflammation¹ and reported reductions in infectious complications for patients.² As it is relatively new, not a lot is known about the stability of SMOF. There appears to be uncertainty as to whether glucose, an essential component of PN required for energy, helps to maintain the stability or causes instability of PN lipid emulsions.³

In order to further investigate the stability properties of each lipid emulsion and to determine what concentrations of glucose are the safest to use in clinical practice, the aim of this project was to compare SMOF and INT emulsions stability when mixed with a variety of glucose concentrations (5%, 20% and 70%) over a period of 5 days (testing every 24 hours). All samples were stored at room temperature (RT) but the higher glucose concentration mixtures were also made and stored at 37°C to investigate the effects of increased temperatures on stability. Laser diffraction, light microscopy, pH testing and visual inspection were carried out to measure any changes in globule size which would indicate changes in stability.

Higher concentrations of glucose were found to reduce the overall pH and increase the presence of larger globules. This explains why 70% glucose caused the most stability issues, especially when stored at 37°C. 20% glucose caused little change in stability and produced consistent results with only a slight decrease in pH. 5% glucose presented with some inconsistent results as some signs of instability were observed by light microscopy but not for visual or laser diffraction tests.

The results concluded that glucose 20% is a safe concentration to use in clinical practice whereas 70% was associated with stability issues. Storing mixtures at 37°C does have an accelerating effect on instability. SMOF was found to be more susceptible to destabilisation than INT.

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Exploring factors influencing student motivation for the MPharm: a qualitative study

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Motivation is a student's willingness, desire and compulsion to participate in and be successful in the learning process. Self-Determination Theory¹ distinguishes between intrinsic motivation, which is motivation which originates from an inherent enjoyment or interest, and extrinsic motivation, which is motivation for a separable outcome or reward. In relation to education, academic motivation is a student's willingness, desire, capabilities and compulsion to participate and be successful in the learning process.^{2,3} Previous research into pharmacy student motivation the UK is lacking, allowing the opportunity for the aim of this project to explore motivational factors which affect students within MPharm IV at Cardiff University School of Pharmacy and Pharmaceutical Sciences (CSPPS).

One-to-one semi-structured interviews using a topic guide devised as a research group of four MPharm IV students. Ethical approval was granted prior to data collection. The topic guide discussed student motivation with regards to Pharmacy, the MPharm degree and commitments outside of university. The interviews were transcribed verbatim and analysed using thematic analysis⁴ identifying main themes and sub-themes.

Twenty-four MPharm IV undergraduate students were purposively selected and interviewed. Nine main themes influencing student motivation were identified from the dataset including Interests, Perceived Relevance, Influence of Others, Previous Experiences, Extra Commitments, Fear, Goals and Timetable.

The objectives were met as student motivational factors have been identified and explored. The results could potentially help other schools of Pharmacy to identify common factors which motivate students in order to promote motivation in their Schools of Pharmacy. Future work could consist of identifying how academics promote student motivation and then compare their methods with motivational factors which increase student motivation. Academics at CSPPS could then develop teaching strategies to increase student motivation and encourage student engagement.

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What are the drawbacks of fluorescent marker pens to measure cleaning efficacy and compliance?

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UV fluorescent marker pens were proposed by Carling *et al.*¹ as a visual means of assessing the quality of terminal cleaning in hospitals. Hospital acquired infections (HAIs; e.g. MRSA and VRE) can survive on surfaces for long periods of time.² Outbreaks of HAIs place a huge financial burden on the NHS due to longer hospital stays, increased medical costs, and the control measures that must be implemented to prevent further spread. The quality and management of hospital cleanliness in the UK has been criticised heavily [3] due to poorly defined guidelines and a lack of microbiological benchmarks.³

The aim of this study was to assess whether or not fluorescent dyes were predisposed to remain on surfaces following wiping and which factors affected dye removal or lack of.

Five replicates of 13 materials, representative of high-touch surfaces, were marked with two types of fluorescent dye (A and B). Surfaces were incubated at 40% or 60% relative humidity (RH) for 2h or 24h. The surfaces were wiped by two types of wipe which were secured to a mechanical wiping device. The amount of dye removed was assessed using a subjective visual 4 scale points (zero scale: no dye present; 4 no dye removed).

Dye A was removed more effectively from surfaces than Dye B by the mechanical wiping device. Mean visual ratings were 1.97 and 2.37 out of 4, respectively. There was no significant difference in the amount of dye removed at 40% and 60% RH. More dye was removed after 2h than 24h; the visual scores were 1.98 and 2.37 out of 4, respectively.

Fluorescent markers are a rapid, simple and cost-effective cleaning intervention¹ that should become the preliminary auditing and training tool in an integrated approach to environmental cleaning which should encompass microbiological standards to judge cleanliness.^{3,4}

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Computer-aided design of a novel generation of BCL-3 inhibitors

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BCL-3 (B-cell lymphoma-3) is a co-transcriptional factor that can bind to two molecules of p50 and forming a tertiary complex with DNA. Once activated, it promotes the transcription of genes that enable cell proliferation and hence a contributing factor in cancer.¹⁻³ JS6 and CB1 are putative compounds previously identified to have activity with the BCL-3/(p50)₂ complex, with the aim of this project to design scaffolds in silico to explore this BCL-3 binding pocket.

A series of computer-aided methods were used, including MOE (Molecular Operating Environment), to create four database libraries (i.e. family 1, family 2, family 3, family 4) discovered from previous research. Docking methods (FlexX, PLANTS and Glide) were used to obtain relative binding positions of these database libraries against the binding pocket. Dynamic methods (Maestro) were used to obtain the binding energies and stability profiles on the final selected inhibitors from each family designed and also on JS6 and CB1.

The docking results showed a large variety in binding positions, with analysis including the best visualised position, their amino-acid interactions and their respectable bond lengths. The best binding poses from each family were analysed by dynamic calculations, in comparison to JS6. Family 3 was the only compound that had stabilised binding within the specified binding pocket, with the exception of family 4 that had interactions in what could be an additional pocket on the BCL-3 protein.

To conclude, prior to researching this further, more experimental research is needed on the BCL-3 protein and the binding pocket identified as there is little detailed knowledge in the literature. Such research could include crystallography and mutation studies. From this, we can aim to have more accurate computer modelling results.

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The adherence of purified *Clostridium difficile* spores (Ribotype 012 and 027) to a stainless steel surface

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Clostridium difficile is an anaerobic, spore forming bacteria. It is a major cause of nosocomial acquired diarrhoea in the UK, and can lead to life threatening complications.¹ Hypervirulent strains exist and include those from ribotype 027.² This study examined three main factors; the effect of different production and purification methods on bacterial spore yield, the effect of the spore purification method on the ability of spores to adhere to stainless steel, a material commonly found in healthcare facilities and the relative adherence of virulent spores (027) versus less virulent (012) spores.

Spores were generated then purified using the methods of Lawley et al¹ (method 1) and Sorg and Sonenshein³ (method 2) and enumerated using a drop-count method.⁴ The strains used were 1801 and R20291 from

ribotype 027 and 630 from ribotype 012. Adhesion to stainless steel was determined using a transfer test in which spore inoculated stainless-steel discs were lowered onto supplemented BHI agar on 16 consecutive occasions and the total spore transfer to the agar surface was calculated.²

Spore yields were affected by the strain and method. From a single experiment, purity level ranged from 97.17-100% for method 1 and 93.49-99.65% for method 2. Tests revealed no differences in adhesion to stainless steel from any of the strains. No difference was found when comparing results obtained in purification method 1 versus method 2. When comparing spores of 1801, adhesion to stainless steel was found to be significantly different ($p < 0.05$) between purified and unpurified spores.

It would thus appear that the degree of purification of the spores affected the degree to which they adhered to stainless steel. Future research is required to establish the best method of spore purification and to determine whether virulent strains adhere more strongly than their less virulent counterparts. Access to such data will improve our understanding of the importance of stainless steel as a vector and determine the feasibility of developing surfaces that prevent adhesion.

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Bacterial adhesion between dental biomaterials and relevant gram positive and gram negative bacteria: Influence of surface and material characteristics via a numerical approach

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Between 2009 and 2010 a study conducted on 6,469 participants found that 85% of adults had at least one tooth filling.¹ With 9% experiencing secondary decay resulting in 26% needing corrective treatment. [1] Raising the question: Do current dental biomaterials have the required antimicrobial properties needed in order to prevent initial bacterial adhesion? With the overall aim being to determine which dental biomaterial(s) are the best at preventing bacterial adhesion and dental plaque formation.

Data was collected via a numerical approach using an in-house developed numerical procedure. Based on the Johnson-Kendall-Roberts (JKR) multi-asperity adhesion model this procedure estimates adhesive forces between two interacting surfaces.^{2,3} Initially adhesive force data was generated for nine dental biomaterials (Zirconia, Glass Ionomer Cement, Hydroxyapatite, Composite Resin, Silver (0.5%, 1% and 5% Ag concentrations), Gold and Cobalt Chromium) in the presence of *Staphylococcus aureus* bacteria. Materials with the greatest and least adhesive force were then identified and adhesive forces were then estimated for these materials in the presence of gram positive (*Streptococcus salivarius* and *Streptococcus mutans*) and gram negative (*Veillonella Parvula* and *Actinobacillus actinomycetemcomitans*) bacteria.

In the presence of *S.aureus*, antimicrobial coating 2 (1% Ag) and hydroxyapatite were identified as the least and most adhesive materials respectively from all biomaterials studied. While in the presence of oral gram positive and negative bacteria *S.salivarius* was identified as the most adhesive bacteria and *S. aureus* the least adhesive bacteria.

Overall, antimicrobial coating 2 (1% Ag) is the least adhesive biomaterial which agrees with its respective surface characteristics. Whereby it has the lowest surface energy value overall biomaterials studied. This agrees with the literature whereby materials with high surface energy values experience greater adhesive forces and vice versa.⁴ Therefore antimicrobial coating 2 (1% Ag) is the best dental biomaterial to use when preventing biofilm formation and secondary decay.

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How can WCPPE best deliver live CPD events for the pharmacy workforce within a rural location?

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Continuing professional development is an important part of maintaining the necessary competence to be a registered pharmacy professional. Organisations such as WCPPE provide opportunities for pharmacy professionals in Wales to continue their learning by holding live events.¹ WCPPE struggles to gain attendances at some of these events, especially in rural locations and as these events are funded by the Welsh government, it means taxpayers money is being wasted.² The aims of this study was to investigate the barriers that prevent registered pharmacy professionals from attending live CPD events held by WCPPE in Powys.

Two focus groups were held at a pre-planned WCPPE event. The focus groups were separated into pharmacists and pharmacy technicians. One focus group contained 7 pharmacists and the other focus group contained 5 pharmacy technicians. The recordings from the focus groups were transcribed and examined, with the key themes from each focus group highlighted.

Eight key themes came out of the focus groups. These key themes were timing of events, location, frequency of events, use of IT, use of learning facilitators, learning and event information, use of expert speakers and communication from WCPPE. A theme quite prominent in the pharmacy technician group was the timing of events with the preference of day time events over evening events and with that the idea of protected learning time in pharmacy contracts. In contrast, a theme that was prominent in the pharmacist focus group was to hold a Sunday study day and discuss 3-4 topics in one day.

The key themes from the focus groups have been used to produce a draft questionnaire which is to be piloted before being sent out to the pharmacy workforce of Powys to gather more data to be able to produce recommendations to improve attendances at WCPPE live events.

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The evaluation of the management of hypnotics in care homes

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In later life many individuals enter care homes to receive care and accommodation; however these settings are often associated with medication errors.^{1,2} Hypnotics are now being deemed 'problem drugs' in this setting.²⁻⁴ The aim of the study is to identify and document the extent of prescribing of hypnotics, as well as the nature and quantity of both prescribing and administration errors in this setting.

A retrospective study was undertaken over 3 months (Jul-Sept) on 12 care homes situated in South Wales. A group consensus on error categories enabled analysis and documentation of medication errors. Two sources of error of 'prescriber' and 'care home administration' were agreed. Within these, areas of: dose, duration, frequency and drug choice were established, each containing further subcategories. Errors were documented and data analysed via SPSS to identify correlations.

Within the 12 care homes and agreed time period 15.02% of residents received a hypnotic. The 44 residents were located in 9 care homes and involved 2768 administrations. 'Duration errors' (58.93%) were the largest contributor to prescribing errors i.e. patients prescribed a hypnotic for more than four weeks. For the care home administration process, on average every three administrations of hypnotics have the possibility of containing an error. 'Frequency attendant errors' (47.33%) i.e. patient administered hypnotic over two hours earlier/later than scheduled, and 'omission' (46.73%) i.e. dose not given, were the largest contributors to care home administration errors. No significant correlation was seen between the total number of administrations a care home conducts and the number of care home administration errors for hypnotics.

Results support views that improvement in both the extent of prescribing as well as the administration of hypnotics in care homes is in need of review. The study enabled an understanding of the pharmaceutical care received by care home residents.

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Design and synthesis of novel opsin ligands to prevent retinal degeneration in Leber's congenital amaurosis (LCA) disease

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Leber's congenital amaurosis (LCA) disease is an inherited form of retinal degeneration disease that cause visual loss mainly in children. It accounts for 3-5% of childhood blindness and affects 180,000 of world's population. 20% cases are due to genetic mutation, RPE65 and LRAT. In LCA disease, there is less formation of rhodopsin that is vital for vision. This is due to mutations that caused less production of 11-cis-retinal, chromophore, to bind tightly with opsin. As a result, it caused accumulation of unbound and misfolded opsin that led to ER stress and eventually retinal cell death.¹⁻² Thus this project aims to develop and synthesise novel opsin ligands to form a stable rhodopsin-ligand complex, in the absence of 11-cis-retinal, to prevent further retinal degeneration.

Bovine rhodopsin was used to study binding interaction between 11-cis-retinal and opsin.³ Eight lead compounds were used for identification of main chemical features for inhibition and binding activities.⁴ Eight new scaffolds were designed and only four were selected based on its conformation and Lipinski's rule of five drug candidates. All compounds were validated and run through molecular docking using Glide docking and Maestro. The end products structure was confirmed using NMR spectroscopy. All scaffolds were synthesised in five synthetic stages: formation of intermediates and conversion to three different groups.

The results show that all scaffolds are able to form interaction with key lysine residue and have consistent binding behaviour. Three scaffolds were successfully synthesised with acceptable yields. Amide group of scaffold 2 shows to be the most potential ligand as it forms more interaction with binding pocket. Scaffold 1 showed to be the least stable and difficult to synthesise.

In conclusion, all four scaffolds showed promising predicted binding mode. All compounds synthesised will be sent for biological evaluation to test for its binding activity and opsin's aggregation.

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Assessing patient inhaler technique in asthma and COPD

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Asthma and Chronic Obstructive Pulmonary Disease (COPD) are diseases of increasing prevalence as there is no treatment as of yet. Inhalers used to deliver aerosolized drugs are the main avenues of therapy in the relief of disease symptoms.^{1,2} However it's well established that patient inhaler technique is generally poor.^{3,4}

The study was conducted in the Cardiff and Vale University Health Board. Patients were recruited from clinics in primary and secondary care settings and their inhaler techniques were assessed. This was done using a Vitalograph Aerosol Inhalation Monitor (AIMs) device. Patients were also asked regarding their condition and any guidance they received regarding their inhalers. The data collected as a group into a Microsoft Excel document for analysis. Statistical analysis was done using a Chi-Square test with the Graphpad Prism 6 program to determine the significance of any differences obtained in the results.

Results found that patients were better at using Dry Powder Inhalers (DPI) (33% fail rate) than pressurized Metered Dose Inhalers (pMDI) (84% fail rate) but were best at using pMDIs plus spacers (9% fail rate). Findings also showed that patients who understood their treatments showed significantly better inhaler techniques than those who did not. (36% vs 67% Fail rate). The above findings were both statistically significant ($p < 0.05$). Findings also showed that patient age, gender and whether a patient was using BOTH pMDIs and DPIs or only ONE of the two had no effect on inhaler technique results. It was also found that the time since a patient last received guidance regarding inhaler technique did not significantly effect a patient's ability to generate good results.

Overall patient inhaler technique was poor. Patients demonstrated better AIMs results when demonstrating DPI techniques compared to pMDI. Competency of healthcare professionals in demonstrating inhaler technique to patients may require a review. An emphasis should be put in ensuring patients understand their treatments and how they help their condition.

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Measuring membrane pores in droplet interface bilayers

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Drug development is greatly assisted by in-vitro artificial mimics of the cell membrane to study the effects of potential drug targets or disease states on lipid-membranes.¹ Droplet interface bilayers can be used to measure current through pores formed in artificial lipid bilayers.¹ The aim was to characterise a pore formed by C-terminus peptide 2 (CTP2) from Bax-Inhibitor 1 (BI-1): a membrane protein that protects the cell from ER stress-induced apoptosis by acting as a calcium leak channel.² At least three C-terminus sequences collectively are suspected to form this channel.² A second aim was identifying if the aspartate at position 209 of BI-1 is essential for pore formation.

Droplet interface bilayers were made by pipetting two aqueous droplets onto two electrodes that were submerged in a lipid containing oil.¹ The amphiphilic lipid made a monolayer around each aqueous droplet. Two monolayers were brought together forming a bilayer. The electrodes enabled a voltage to be applied and an ionic current across the bilayer was measured using a patch clamp amplifier.³

When CTP2 was compared to a fixed conductance pore forming protein called α -hemolysin, and variable conductance pores formed by electroporation, there were close similarities to electroporation. Histograms revealed that there was a characteristic spread in current suggesting the pore may vary in size. On mutating the aspartate at position 4 to an alanine the amount of current transmitted was significantly reduced.

CTP2 forms a pore that resembles the activity of electroporation. This suggests it may form a toroidal pore that varies in size. It has stochastic transient action; but once formed, tends to stay in the bilayer and likely transports calcium. On mutating the aspartate at position 4 current transmitted is reduced but not stopped, suggesting that aspartate is probably important but not essential for pore formation.

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Redistribution of patient returned prescription medicines: what's stopping us? The patient's view

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The redistribution of patient returned prescription medicines (ROPRM) is a concept that has been investigated by several studies already.¹⁻³ It is popular within healthcare academia as it would reduce waste and this may ease the strain on local NHS Trust budgets.⁴ In order for the concept to become a practice, it is important to gauge how patients themselves may view it. As previous studies have focused on the healthcare professional's stance on drug redistribution, this paper aims to provide an alternate perspective on the idea by gathering and analyzing the opinions of a sample of the local people. Interviewing people about the topic enables the researcher to ascertain whether such a scheme would be received and reacted to positively or negatively.

Participants were randomly sampled from GP practices within the Cwm Taf University Health Board (CTUHB) and sent out invitation letters, 11 participants responded who were able to take part in the study. Semi-structured interviews were held at the participant's local GP practice, these were recorded and later transcribed.

Thematic analysis of the transcriptions proved the qualitative interviews were successful in getting an idea of how receptive the patients in the Cwm Taf area are to the idea of ROPRM which was positive overall, but raised some concerns about the hypothetical rolling out of ROPRM: risk of tampering, damaged packaging, storage conditions of medicines in the previous patient's possession, the opportunity of fraud, certain forms of medicines returned being unacceptable (liquids, inhalers), the cost implications and cross-contamination. These coincide with barriers that have arisen in previous research. However, unlike previous research conducted with healthcare professionals few solutions for these barriers were suggested, which is understandable due to patient's lack of knowledge on prescription medicines.

The concept of consent was identified in this study which had not been previously reported, where patients discussed whether they would personally want to know if they were receiving returned medicines and came to conclusions that it is likely that the public would need to be informed of ROPRM. Patients agreed they would have to put trust in the healthcare professionals to ensure the quality of returned medicines still meets standards. Future research is necessary to solve patient's concerns as well as taking ROPRM to a wider audience of patients to find more generalizable results.

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Canonical Wnt signalling in murine models of Alzheimer's disease

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Accumulation of beta-amyloid (A β) which is cleaved from amyloid precursor protein (APP), is a central event in Alzheimer's disease (AD) neuropathology.¹ A relationship between A β -induced neuronal dysfunction and dysregulation of the canonical Wnt signalling pathway has been observed in AD.² There is some evidence that A β may downregulate the Wnt pathway, however it remains unclear whether Wnt signalling is up or downregulated in AD.³ Recent research has suggested activating Wnt signalling may be a novel therapy for AD.⁴ This study investigated whether key canonical Wnt protein levels are up or downregulated in transgenic (Tg) PDAPP murine models of AD which overexpress APP and accumulate A β with age.

Western blotting was used to compare levels of APP, beta catenin (total and non-phosphorylated), GSK-3 α , GSK-3 β and TCF7L2 in cortical tissue extracted from 3, 11 and 18 month old Tg mice and their wild-type (Wt) litter mates. The changing patterns of protein levels with age were also compared within genotypes.

APP was overexpressed in all Tg mice. Although no changes in levels of total beta catenin were observed, the non-phosphorylated form was increased in 18 month old Tg mice when compared to 18 month old Wt mice. Levels of non-phosphorylated beta catenin decreased with age in Wt mice, however, Tg mice did not demonstrate this decrease with age. No differences in levels of GSK-3 α , GSK-3 β or TCF7L2 were observed.

The raised levels of non-phosphorylated beta catenin imply there is an upregulation of Wnt signalling in Tg murine models of AD compared to Wt mice. Since this was only observed in the oldest mice it is likely to be an amyloid-related effect. The results of this study highlight that the activation of Wnt signalling as a therapy for AD should be treated with caution.

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Changes in hypnotic and anxiolytic prescribing in Wales following introduction of an educational pack

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The prescribing of hypnotics and anxiolytics was much higher in Wales compared to England in 2010.¹ An educational pack was produced in April 2011 by the All Wales Therapeutics and Toxicology Centre in order to reduce the number of hypnotics and anxiolytics being prescribed in Wales.² The aim of this study was to investigate whether there was a change in prescribing trend in the twelve months following the intervention compared to the previous twelve months and whether there was a change in the number of drug related deaths associated with these drugs.

An Auto Regressive Integrated Moving Average Interrupted Time Series analysis was used to assess whether there were significant changes in prescribing trend pre and post intervention. Data were collected for benzodiazepines, Z drugs, pregabalin and gabapentin in terms of number of Defined Daily Doses prescribed per 1,000 patients per month from May 2010 to April 2012 for Wales as a whole and for each anonymised health board. A Fishers' Exact test was used to compare the Fatal Toxicity Index of the drugs pre and post intervention for Wales, using England as a control group.

There was a statistically significant decrease in the prescribing trend of Z drugs in two health boards in Wales ($P=0.047$, $p=0.017$), and a statistically significant increase in the prescribing trend of gabapentin in two health boards ($p=0.002$, $p=0.024$) in the twelve months' post intervention. There was no statistically significant change in the number of drug related deaths post intervention.

The changes seen in prescribing trend cannot be directly linked to the intervention due to the quasi experimental nature of this study³ as the contribution of other confounding factors that may influence prescribing trend cannot be accounted for. Despite this, the educational pack is still a useful resource for hypnotic and anxiolytic reduction strategies.

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Evaluation of patient's inhaler technique in the Cardiff and Vale Univeristy Health Board

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Inhalers currently play a major contribution in treating asthma and chronic obstructive pulmonary disease (COPD), and will remain to do so in the future.¹ Asthma and COPD are amongst the most common chronic diseases in the world and are a major and growing health concern in the UK.² Evidently inhaler technique is poor in the general public and in healthcare professionals.^{3,4} The aim is to evaluate the quality of inhaler technique in asthmatic and COPD patients of the Cardiff and Vale University Health Board.

Convenience sampling was used in order to recruit participants. Structured interviews comprising of a questionnaire, and inhaler technique assessment were carried out. Quantitative data was entered into Microsoft excel, and frequency analysis was carried out. Statistical analysis was performed by using GraphPad Prism, using chi squared analysis. All data was anonymised. Both ethical approval and NHS service evaluation was granted prior to commencing.

61 participants were recruited. Inhaler technique was poorest in MDI users with 83% demonstrating poor technique, compared to 17% (DPI users). Most participants (46%) were last demonstrated how to use their inhaler(s) over a year ago, with 15% never receiving guidance on how to use their inhalers correctly. Majority (75%) of participants were last educated by nurses. Pharmacists are massively underrepresented in terms of who is giving advice to patients, with only 2% of the participants previously having received guidance from a pharmacist.

Participants' inhaler techniques were generally poor. Using a MDI combined with a spacer provides potential for improvement in poor technique seen in MDI users. Thorough education and training is essential in order for participants to use inhalers correctly. The quality of technique rapidly deteriorates and therefore active re-education is critical to maintain correct technique.

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Evaluation of patient's inhaler technique in the Cardiff and Vale University Health Board

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Five million people suffer with asthma and 3 million with COPD in the UK.^{1,2} Inhalers are the leading form of treatment used to treat these conditions,³ providing local effective treatment to the lungs, however, they can be difficult to use, with studies reporting up to 90% of people use their inhalers incorrectly.⁴ This study aims to assess patient's inhaler technique within the Cardiff and Vale University Health Board and assess patient's understanding of how their prophylactic inhalers help their condition.

Patients were recruited from GP surgeries, respiratory clinics and Cardiff University Students Union. Patients were questioned on their use of their inhalers and understanding of how their prophylactic inhalers help their condition, through a structured interview. AIMS (Aerosol Inhalation Monitor) VitalographTM Devices were then used to assess patient's technique. Chi-squared (χ^2) tests were used for analysis with statistical significance accepted at $p < 0.05$.

A total of 61 patients agreed to participate in the study. pMDIs were misused by 30 (84%) subjects with only 5 (17%) DPI users and 2 (10%) subjects who used a pMDI with a spacer obtaining a fail result ($p < 0.0001$). Of the 52 subjects who had received tuition on inhaler technique, 39 (75%) last received tuition from a nurse with only 1 (2%) from a pharmacist. A total of 38% of patient showed no or incorrect understanding of their prophylactic

inhalers, with only 9% describing the preventative treatment in some depth.

Generally inhaler technique is poor, and is significantly problematic in pMDI use, throughout the population. Data from this study suggests that current methods of education on technique are ineffective and training of HCPs are currently inadequate. Patients are not currently consistently informed on their use of inhaled medications. Future research into improving patient technique training needs to be considered.

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Design and synthesis of new focal adhesion kinase inhibitors for metastatic breast cancer

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Breast cancer is the most common cancer in the UK, with 1 in 8 women diagnosed in their lifetime.¹ Metastatic breast cancer is a particular problem, with a 5-year survival rate of just 15%.¹ Focal Adhesion Kinase (FAK) is a tyrosine kinase involved in cell signaling. It is up-regulated in several advanced stage tumors and promotes tumor progression and metastasis through its effects on cell adhesion, migration, proliferation and survival.² The antihistamine chloropyramine was found to inhibit the interaction between FAK and another tyrosine kinase important for cancer cell survival and tumor progression: vascular endothelial growth factor receptor 3 (VEGFR3).³ Anticancer activity resulted both *in vitro* and *in vivo*, but at moderate concentrations.³ This project aimed to design and synthesize a range of potent chloropyramine analogues that inhibit the interaction between FAK and VEGFR3.

Design of compounds was informed by previous work on structure activity relationships of chloropyramine analogues and synthetic feasibility.⁴ 2 general structures with different modifications were designed. Molecular modeling was used to predict the strength of interactions between the compounds and the region of FAK where VEGFR3 binds. Compounds were synthesized via a 2-step process of reductive amination followed by either base-catalyzed acylation or alkylation.

Several of the compounds were found to have better predicted binding interactions than chloropyramine. All intermediates were successfully synthesized. Of the acylation final products only 1 was successfully made and all alkylation final products were unsuccessful, being double alkylated to form quaternary ammonium compounds.

A range of new compounds that appear to be able to inhibit the FAK/VEGFR3 interaction have been designed. Initial attempts to synthesize these were not entirely successful and procedures need to be repeated to optimize conditions. All compounds will be tested for activity in several breast cancer cell lines.

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Exploring pharmacists' views on the integration and use of e-DAL within the community pharmacy setting

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Communication of medication changes between care settings presents a significant risk to patient safety upon discharge from hospital.¹ A Discharge Advice Letter (DAL) containing clinical information is sent to their General Practitioner (GP) but not to their Community Pharmacist (CP). In Wales, CPs can complete a Discharge Medicine Review (DMR) upon receipt of the DAL, reviewing the patient's medication after discharge.² Currently in Wales, electronic discharge advice letters (e-DALs) and electronic discharge medicine reviews (e-DMRs) are piloted in 42 community pharmacies; e-DALs are sent directly to CPs via the Choose Pharmacy Application (CPA). The aim of this project was to explore whether or not community pharmacists consider e-DALs and e-DMRs provided via the CPA to be effective.

A qualitative approach was used for this study. Face-to-face interviews were deemed most appropriate using semi-structured interview technique to explore participants' thoughts, behaviours and experiences.³ The research was conducted by two research students. Interviews were recorded permitting sharing of transcripts between the researchers. The data was analysed separately using thematic analysis.

A response rate of 48% was achieved: seventeen pharmacists piloting the e-DAL and e-DMR scheme were interviewed. The majority of participants believed that e-DALs were superior to paper DALs but required further amendment. Their views confirmed the need to improve communication between healthcare practitioners to ensure continuity of care when a patient is discharged from hospital. These correlate to the recommendations stated by the Royal Pharmaceutical Society.

Implementation of e-DALs and e-DMRs could improve the transition from secondary to primary care. Granting CPs access to patients' discharge information may improve continuity and patient care. Evidently, DALs provide the highest quality of care to patients but must be delivered to the appropriate healthcare practitioners if they are to be effective.

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Identifying and exploring factors affecting student motivation for the MPharm: a qualitative study

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When an individual is "moved to do something" they are considered motivated.¹ Motivation is an important concept for educators to understand. Motivation is an essential requirement for learning and lack of motivation within learning environments can have detrimental effects on student performance.² Self-Determination Theory (SDT) distinguishes between two types of motivation. Intrinsic motivation is adopted when individuals participate in an activity due to interest. Extrinsic motivation is adopted to achieve a separable outcome.¹ Research has shown that self-efficacy is effective for predicting students' motivation.³ The aim was to explore, identify and analyse factors that affect the motivation of final year pharmacy undergraduates at Cardiff School of Pharmacy and Pharmaceutical Sciences (CSPPS).

Final year MPharm undergraduates were identified using purposive and convenience sampling. The team of four researchers produced a topic guide after reviewing and discussing the literature and MPharm topics. CSPPS ethical approval was obtained for the topic guide, consent form, recruitment email and participant information sheet. Pilot interviews were conducted between the four researchers and transcribed verbatim. Semi-structured interviews were audio recorded with written consent. Interviews were transcribed by Virtutype, anonymised by each researcher and shared between the four researchers for independent, thematic analysis.⁴

Twenty-four final year MPharm undergraduates participated. Eight themes were identified from the data: Assessments, Influence of Others, Final Year Project, Fear, Subject, Teaching Sessions, Plans After

Graduation and MPharm Structure. The results showed that students have both intrinsic and extrinsic motivation.

Motivation differs between students depending on individual preferences, personal circumstances, current aims and goals for the future. The results of this research may be used by the CSPPS to improve student motivation, which may lead to improvements in student and school performance. A possible area for future research may include researching the motivation of final year MPharm undergraduates in other UK Pharmacy Schools.

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Rivastigmine usage in Lewy body dementias

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Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) are similar diseases which present with motor and cognitive impairments.¹ Rivastigmine, a cholinesterase inhibitor, can be used to treat the cognitive symptoms experienced in these diseases.² The aim of the study was to explore the effect of Rivastigmine use in PDD and DLB as it has not been thoroughly investigated.³

Data on PDD and DLB patients were extracted from 'The Electronic Clinical Network Parkinson's Disease and Related Disorders Database'. This database contained information on patients who attended movement disorder clinics at two different hospitals in Wales between 2000 and 2015. The demographics and level of motor and cognitive impairments were explored in PDD and DLB patients. We then explored any links with these findings and Rivastigmine use. The effect of Rivastigmine was measured through Clinical Global Impression (CGI) which assesses motor function, cognitive function and aspects of daily living. It was also measured through cognitive test scores which included Mini-Mental State Examination (MMSE) and Addenbrookes Cognitive Examination-Revised (ACE-R).

292 patients were included in the study. 84% were PDD and 16% were DLB patients. Both disorders were more prevalent in males. PDD patients demonstrated greater motor impairments and DLB patients demonstrated greater cognitive impairments. Only PDD Patients currently taking Rivastigmine scored higher in MMSE compared to those who had previously or never taken Rivastigmine. ACE-R scores did not vary in relation to Rivastigmine use in either PDD or DLB patients. In terms of CGI, the only patients who demonstrated an improvement were either currently or previously taking Rivastigmine.

Rivastigmine may improve cognitive function in PDD patients. The effect of Rivastigmine on cognitive function in DLB patients is unclear. However, Rivastigmine usage appears to be beneficial in PDD and DLB patients by having a positive impact on CGI.

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Analysis of Welsh plant extracts to find novel glioma treatments

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Plants have been known for their medicinal properties for thousands of years. Hippocrates the renowned Greek physician advised the use of certain plants to treat uterine tumours.

Two samples were obtained from native Welsh plants, from a reverse osmosis concentrate, which had been treated with 2.5% cellulase enzyme addition and a fluid sample taken from a tank of decomposing plants,

which had been naturally composting for around two years, were extracted using ethyl acetate. The extractions were analysed using different techniques, such as, analytical thin layer chromatography, preparative chromatography, size exclusion chromatography and mass spectrometry. A web application, LLAMA was used to suggest drug-like products *in silico*.

The presence of secondary metabolites was determined by mass spectrometry. LLAMA generated 1649 products, of which 785 had logP values between 1.5 and 2.7, but none had a polar surface area suitable for blood brain barrier penetration.

The membrane poration of droplet interface bilayers with an EGFR derived cell-penetrating peptide, EJP-18

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Delivery of drugs intracellularly is a vast area of research, which has been aided by artificial bilayers, for the observation of energy-independent processes. Droplet-interface bilayers (DIBs) are a recent, more stable system.¹ Hundreds of cell-penetrating peptides (CPPs) are being studied due their ability to internalise cargoes.² This study aims to use DIBs to increase knowledge of the penetration mechanisms of EJP-18, a new CPP derived from a receptor tyrosine kinase. If EJP-18 forms membrane pores, subsequent permeability can be recorded.

This study makes electrophysiological measurements of CPP-induced pore formation in DIBs, when a fixed potential is applied across the membrane. This method was first validated with protein pore alpha hemolysin before the well characterised CPP octaarginine (R8).³ Secondly, EJP-18 was investigated. The DIB technique creates a bilayer between two aqueous droplets suspended on agarose coated electrodes in an oil/lipid environment.⁴ Conductance data was analysed to confirm bilayer formation and observe poration.

Controls of stable bilayers without peptide, electroporation and fixed conductance pores with α -hemolysin were characterised, as seen previously. Both R8 and EJP-18 formed pores between 2-20 μ M at lower potentials than electroporation, with poration that was similar in nature. Lengthened bilayer formation was observed. With EJP-18, higher concentrations caused increased conductance, large variability in poration states across time occurred and no difference in conductance seen between positive or negative applied potentials.

Lengthened bilayer formation suggests CPP disrupts the monolayer. Escape of R8 through micelle formation during incubation is hypothesised. EJP-18 induced pores are variable, stochastic and transient in nature which may indicate mixed pore-forming translocating mechanisms. While energy-independent model membrane disruption is clear, translocation is not conclusive though likely from the extent of membrane permeability. Total Internal Reflection Fluorescence Microscopy would image pore nature and size and EJP-18's translocation and interactions.⁴

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The evaluation of the management of medications containing paracetamol in care homes

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There has been some evidence that care home residents are experiencing suboptimal pain management, particularly those with cognitive impairment.¹⁻³ The aim of this study is to evaluate the prescribing and management of medications containing paracetamol in care homes.

A literature review was conducted to determine the issues faced by medications containing paracetamol in care homes. Provisional error categories were then agreed upon and piloted on a set of data from the 19th of October 2015. With the results of the pilot study, a group consensus was achieved on the error categories that was feasible and the error categories were finalised. The analysis was carried out on data for the period of 1st July - 31st September 2015. The SPSS statistical package was applied to determine if there is a correlation between the total number of administrations and the total number of care home errors for medications containing paracetamol.

A total of 24356 administrations were given to 123 patients over the three-month period. One prescribing error was identified, while 6848 care home errors were found. "Dose-Omission" and "Frequency-Attendant" errors contributed the significant majority of errors. A statistically significant ($p < 0.05$) positive correlation was found between the total number of administrations and the total number of care home errors for medications containing paracetamol.

Almost all errors were care home related, with omissions contributing to nearly half the errors identified. This is supported by the Care Home Use of Medicines Study (CHUMS) which found that 49.1% of error were due to omissions as well.⁴ The statistically significant positive correlation can be explained by the high number of administrations, where a high number of administrations will tend to lead to a higher number of errors. In conclusion, the management and prescribing of medications containing paracetamol needs to be drastically improved.

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Exploring the public's opinion of medication wastage, cost and attaching a price to dispensed medication labels

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Approximately £300 million is wasted on partially or completely unused prescribed medication every year in the UK.¹ The Government has proposed introducing a price on dispensed medication labels to increase adherence and reduce waste. MPs claim this intervention could save the NHS £100 million a year.² The primary objective of this study was to explore the public's reaction to including the NHS cost of prescribed medicines on the dispensing label.

Focus groups were conducted in order to allow discussion of opinions on the cost and waste of prescribed medications and the addition of the medication price on the dispensing label. A purposive sample of participants were recruited from key population groups to take part in focus groups via a gatekeeper. Focus group discussions were audio recorded and transcribed verbatim. The data was thematically analysed and key themes were generated.

Thirty-four participants took part in six focus groups. The six emergent themes were: knowledge of the problem; barriers to adherence; motivations for adherence; prescribing issues; patient-centered care; and overall reactions to proposal. Participants suggested that better communication between patient and prescriber about medication and their concerns would help improve wastage rather than adding the price on the label: "*It's about putting things into context for the patient and the patient understanding exactly the benefits of what they're taking and having that really good patient-centered conversation*" STP3. Furthermore, different reasons for non-adherence to medication were identified by participants, on which knowing the medication cost would have little impact: "*So the reason you would not take a medicine is either because you forget- knowing the cost won't make your memory better -or because you feel better and you don't need it.*" STP2

The overall consensus was that the participants did not think that including the price on the dispensing label of prescription medication labels would help to increase adherence and reduce waste. The proposal hoped to tackle medicines wastage by making the public aware of the cost of medicines. One of the root causes of

wastage was identified to be non-adherence, therefore if this is not tackled, the proposal to make the public aware of the cost of medicines may be ineffective.

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Evaluation of patients' inhaler technique in the Cardiff and Vale University Health Board

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Inhalers can be used to treat respiratory conditions, and they are beneficial as they deliver medication directly to the target site of action, the lungs.¹ Good inhaler technique is required to get drug deposition in the lower airways. Inadequate technique can therefore lead to suboptimal dose delivery.² This study aims to evaluate asthma and chronic obstructive pulmonary disorder (COPD) patients' inhaler technique in the Cardiff and Vale University Health Board (UHB).

The study was approved as a service evaluation by Cardiff and Vale University Health Board and ethical approval was obtained from the Cardiff School of Pharmacy and Pharmaceutical Sciences ethics panel. A structured, quantitative interview form gathered information about the patients' current prescribed inhaler(s) and their use. Technique on a pressurised metered dose inhaler (pMDI) (with or without a spacer) and dry powder inhalers (DPIs) were assessed using a Vitalograph AIM™ device which predicts drug deposition in the lungs. The anonymous data was collated to enable frequency analysis and Chi-squared statistical tests.

Of all patients assessed, only 26% managed to achieve good inhaler technique. The standard of technique was device dependant ($p = <0.05$). Only 17% of DPI assessments obtained a fail result, compared to 83% of patients on a pMDI. Using a spacer with a pMDI reduced fail results to 9%. No other factors, including technique training and different patient subgroups, had any significant impact on the standard of inhaler technique ($p = >0.05$).

Overall, inhaler technique is of a poor standard amongst patients in the Cardiff and Vale UHB. The standard of technique is device dependant. Current HCP advice does not appear to impact on the success of patients' inhaler technique, and the current opportunities to educate patients on good technique are not being utilised and fully optimised.

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Comparing tau phosphorylation in models of Down Syndrome and Alzheimer's disease

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Alzheimer's disease (AD) is a progressive, neurodegenerative disorder.¹ Amyloid Precursor Protein (APP) is cleaved to form neurotoxic beta-amyloid (A β).² A β activates kinases DYRK1A and GSK-3 α / β which phosphorylate tau, contributing to the development of neurofibrillary tangles and neuronal cell death.³ My aim was to compare differences in protein levels of APP, DYRK1A, GSK-3 α and β , and phosphorylated tau (residues Thr²¹², Ser³⁹⁶/Ser⁴⁰⁴), and total tau across 4 littermate mouse lines: Tg2576 (AD model), Tc1 (Down syndrome model trisomic for human chromosome 21 but lacking APP), 'Double' (offspring of Tg2576 and Tc1), and wild-type (Wt) as controls. The 'Double' mice were studied to illustrate that these mice would demonstrate changes in protein expression as a product of their parents' protein expression.

Mice brains were harvested at 10 months old. Cortical brain tissue was extracted and protein levels were measured using Western blotting. Data were analysed using one-way ANOVA, followed by Tukey's post-hoc test.

Overexpression of APP was significant and confirmed transgenicity of Tg2576 and 'Double' mice. Changes in kinase levels and corresponding levels of phosphorylated tau were not significant across groups.

Data collected suggests that increasing APP levels did not affect the kinases and phosphorylation sites studied, but there are a number of variables which limit the conclusions which can be drawn. Future work may include using older mice, looking at the active form of the kinases and other kinases, and working with alternative mouse models. This study, however, supports reviews that other mouse models should be used in the study of Down syndrome, and also highlights the importance of using an established genetic background in animal research⁴ as the mice had a unique background due to the Tg2576/Tc1 cross.

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Identifying and exploring factors affecting student motivation for the MPharm

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Motivation is the driving force that drives a person towards a goal.¹ There are many published studies examining motivation but few that examine motivation in UK MPharm courses.² Understanding motivation is key to augmenting a student's motivation in their studies. This investigation aims to identify and explore factors which may affect student motivation for the MPharm at Cardiff University.

The research group of four final year MPharm students with a project supervisor designed a qualitative investigation to explore the project title. Semi-structured interviews were conducted with purposively sampled 4th year MPharm students at Cardiff School of Pharmacy and Pharmaceutical Sciences. Interviews were conducted on 24 participants using one to one interviews. Each researcher conducted a pilot interview with a fellow researcher and transcribed that interview. Then a list of potential participants were developed, the researcher then interviewed an additional five participants each, these interviews were recorded and transcribed verbatim by Virtuetype®, anonymised and checked by the researcher before sharing with the research team to individually thematically analyse.³ Ethical approval was obtained.

Twenty-four participants were interviewed and six themes were developed from the data: '*Failure*', '*Structure of MPharm course*', '*Feedback and Guidance*', '*Perceived relevance*', '*Effort*' and '*Interest*'. Students had expressed many factors that affect their motivation and to what degree with the majority having a strong intrinsic drive towards their studies.

The investigation highlights that no student is the same, motivation is an important and multifaceted element of an MPharm student's studies. It is important to consider both positive and negative motivational factors to better understand why a change is effective. Findings from this investigation should be considered to investigate motivational factors in more of the MPharm student population in the UK.

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Solid phase extraction of natural compounds from Greek marine sponges

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Natural compounds extracted from marine sponges are evidently structurally unique and possess various pharmacological activities.¹ However, the environmental niche of marine sponges and the lack of understanding of its matrix complexity poses a hindrance towards marine sponge drug development.¹ This

research experiment aims to use a chemoselective isolation by utilization of electrophilic sulfonyl chloride and isothiocyanate resins to extract natural compounds from Greek marine sponges.² It is hypothesized that most natural compounds from marine sponges contain nucleophilic functional groups which can be extracted through electrophilic solid phase extraction.³ The objective is to obtain as much natural compounds as possible from Greek marine sponges through a solid phase extraction technique.

Extracts from the sponge *Chondrilla nucula* and a *Sarcotragus* sp. were neutralized to remove charge polarity. Sulfonyl chloride and isothiocyanate resins were swollen and sponge samples were added. The resin loaded with natural compounds was subjected to cleaving agents to obtain the natural compounds which were tested with mass spectrometry for the presence of compounds.

Isothiocyanate resins cleaved in neat trifluoroacetic acid showed high yields of recovery but limited types of natural compounds. Sulfonyl chloride resins cleaved with diethylamine followed by sodium hydroxide shows the largest diversity of compounds extracted, however yield percentage ratio is low. Mass spectrometry shows that compounds were recovered from the solid phase extraction.

The solvent used affects yield ratio but not the variety of compounds extracted. Electrophilic resins and cleaving agents are able to scavenge nucleophilic natural compounds from Greek marine sponges and give rise to contrasting natural compounds obtained. Solid phase extraction was demonstrated to be successful in recovering natural compounds from Greek marine sponges albeit a less efficacious method due to low yield ratios in combination with salts present.

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Using optical coherence tomography as a novel method to characterise the puncture of hypromellose hard-shell capsules in a RS01 monodose dry powder inhaler

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Dry powder inhalers (DPI) deliver drugs to the lungs upon breath-actuation and are becoming increasingly accepted for pulmonary drug delivery for local and systemic applications. Some DPIs emit powder from a punctured capsule. The puncture morphology may affect the subsequent delivery and deposition of drug after inhalation. Previous characterisation of punctures has used two-dimensional imaging (microscopy).¹ The aims of the project were to characterise three-dimensional features of punctures in hypromellose capsules using Optical Coherence Tomography (OCT) and to determine the effect of the inhalation event on this puncture morphology.

A method was developed, characterising capsule puncture by a Monodose RS01 DPI (PlastiApe, Italy) using multi-beam swept-source frequency domain OCT. Inhaler testing apparatus (inhaler adaptor, Next Generation Impactor™ (NGI™), flow meter and vacuum pump) was used to simulate an inhalation event and OCT images were taken both before and after simulated inhalation to investigate the effect of inhalation on puncture characteristics. The project examined twenty empty capsules conditioned over calcium chloride and twenty empty capsules conditioned over magnesium nitrate to determine performance at the lower and higher ends of the normal moisture specification range. Five capsules containing a model budesonide and lactose formulation were also examined and the NGI provided delivery and deposition information.

OCT imaging was able to successfully determine the angle of the flap created in capsules following puncture by a DPI. Capsules showed an overall decrease in the angle of the flap created in capsules imaged before ($34.8^\circ \pm 11.0$) and after a simulated inhalation event ($30.2^\circ \pm 10.1$). Formulation containing capsules showed no significant difference between the flap angles before ($51.8^\circ \pm 7.0$) and after ($50.4^\circ \pm 7.3$) simulated inhalation.

OCT imaging can provide sub-surface information about a capsule puncturing event and enables the position of the flap to be determined. Results indicate that the positioning of the flap created in capsules is variable. Punctures may also be affected by an inhalation event. The lack of statistical power limits the clinical significance

of the results but the use of a novel imaging system to capture information about the three-dimensional positioning of the flap provides encouraging possibilities for further DPI research.

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An exploratory study of student engagement on the Cardiff MPharm degree programme

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In higher education, there has been a recent focus on the enhancement of learning. After exploring the impact of 'the student experience' and 'research-led teaching' on educational outcomes, educators are addressing student engagement as a factor of student learning.¹

Student engagement is the: "*interaction between the time, effort and other relevant resources invested by both students **and** their institutions intended to optimise the student experience and enhance the learning outcomes and development of students and the performance, and reputation of the institution.*"¹

The aim of this study was to assess the level of engagement of pharmacy students on the Cardiff MPharm degree programme.

A self-completed survey² was distributed to year 2, 3 and 4 students who participated anonymously. The survey consisted of 15 likert-scale questions and 3 qualitative free text comment boxes, all questions explored four domains – critical thinking, course challenge, collaborative learning and academic integration. It was distributed during lecture/workshop slots by purposive sampling. The quantitative data was analysed using SPSS, the qualitative data was exported into a word document and an inductive thematic analysis was undertaken retrospectively. Comparisons were made between the years with respect to the four domains using a one-way ANOVA test with Bonferroni post hoc test. Comparisons were also made within the years looking at student engagement of males versus females using a 2-tailed paired T test. Ethics approval was obtained for all of the above.

The course produced positive engagement in three domains but not in the fourth (academic integration). The course challenge and level of academic integration were consistent in all years with no statistically significant differences being observed. Year 1 and 3 students engage more often in critical thinking compared with year 2 students. Year 3 students engage most often in collaborative learning. In all years, female students find the course more challenging than male students. In year 2, male students communicate more with the staff, on the contrary, year 3 female students communicate more with the staff than male students.

In conducting this study, it has become evident that Cardiff School of Pharmacy has produced an MPharm programme that by this measure delivers engagement in three domains, however, future work should focus on academic integration, in other words, the relationship between staff and students.

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Formulation of mucoadhesive films for the simultaneous delivery of chlorhexidine and diclofenac in the treatment of periodontal diseases

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The aim of this study was to formulate a mucoadhesive polymeric film containing chlorhexidine and diclofenac as a new treatment for periodontal diseases. Chlorhexidine has broad-spectrum activity against Gram-positive and Gram-negative bacteria¹, and is approved to combat biofilm². Simultaneous delivery of an antiinflammatory would reduce pain.

Three drug loaded thin films were prepared using a polymer mixture³ containing 10mg diclofenac alone, 25mg chlorhexidine alone and 10mg Diclofenac/25mg Chlorhexidine (DCX) in combination. In vitro diffusional release properties were investigated. Microbiological testing was carried out to determine the antibacterial

potential against planktonic form and in a biofilm model. The test organisms included three *Streptococcus* species, *P.gingivalis*, *F.nucleatum* and *A.actinomycetemcomitans*.

Chlorhexidine release was low at up to 4%, whereas diclofenac release was more rapid and reached 56% within 30min. Chlorhexidine was active and acting at an inhibitory level against all test microbes. A range of 3-6 log₁₀ reductions in biofilm cell recovery was seen after exposure to all films containing chlorhexidine. No antibacterial or potentiation activity was observed for diclofenac.

Low release of chlorhexidine was attributed to interaction with the polymer matrix; however, the film demonstrated inhibitory effects against all test bacteria. Limited chlorhexidine release is beneficial regarding potential cytotoxicity⁴. Overall, this study supports further investigations into the antibacterial and antibiofilm properties as a product to treat periodontal diseases.

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Using optical coherence tomography (OCT) to evaluate the puncture of gelatin capsules by a DPI

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Dry powder inhalers (DPI) are devices that deliver active pharmaceutical ingredients (APIs) to the lungs in the form of a dry powder.¹ A two-piece capsule is frequently used as the dose-holding system for the DPI. Capsules for DPIs are often made from gelatin or hydroxypropyl methyl cellulose (HPMC). Unit dose DPIs are designed to puncture capsule shells to enable powder release upon patient inspiration. Following puncture a 'flap' is often created in the capsule shell adjacent to the puncture site.² Little is known about the position of this flap, or the effect it may have on powder release and hence inhaler performance. This study aims to use optical coherence tomography (OCT) to gather three-dimensional information about the capsule puncturing event in gelatin capsules in order to determine the angle of the 'flap' created. A secondary aim is to determine any changes in the position of the flap following an inspiration event.

Gelatin capsules were conditioned over calcium chloride or magnesium nitrate for 2 weeks. This provided capsules at the lower and upper end of the normal moisture specification range.³ The conditioned capsules were loaded into a RS01 Monodose DPI (Plastiape, Italy) and punctured. After puncture with a single pin in each end of the capsule the capsule was scanned using OCT. The capsule was then re-positioned in the inhaler, which connected to an NGI associated with a vacuum pump. The vacuum pump was switched on and created a flow rate of 60L/min for 4 seconds to simulate an inhalation event. Capsules were then removed from the inhaler and re-imaged with OCT. OCT data were analysed using ImageJ software.

OCT provided a non-destructive method to determine the position of the capsule flap below the capsule surface. There was no significant different in the angle of the gelatin capsule flap before and after the simulated inhalation event. Almost 50% of gelatin capsules that were conditioned at the lower humidity also had evidence of damage to the shell following the simulated inhalation event.

The study indicates that the angle of the flap created in gelatin capsules by a DPI is not affected by an inhalation event. Future work should evaluate a larger sample size to confirm the finding. The variability of the flap angle was also notable and this also warrants further investigation.

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Adhesive interactions between antimicrobial coatings and gram positive (*S. aureus*) and gram negative (*E. coli*) bacteria: influence of surface energy and material properties

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Bacterial cell adhesion to materials is the first step in the formation of a biofilm. The adhesion of bacteria to hospital medical equipment, medical devices, food processing equipment and packaging has been recognised as a widespread problem causing infectious diseases.¹ Since microbial adhesion to materials is a prerequisite condition for biofilm production, prevention of microbial adhesion on equipment surfaces will have a major impact in preventing biofilm formation. An approach is to modify surface properties of materials to make the less attractive to microorganisms.² The aim of the research was to find out the influence of surface energy parameters and material properties of antimicrobial coatings.

A numerical procedure developed by Prokopovich and Perni³ was used to estimate the adhesive interactions between various antimicrobial coatings and *E. coli* ATCC 25922 or *S. aureus* NCTC 8532. The Johnson-Kendall-Roberts (JKR) model was used to predict the forces of adhesion between the antimicrobial coatings and bacteria. Contact between real surfaces is carried out by the asperities on the surfaces. Each asperity was assumed to be hemispherical and had a height and a radius. Different antimicrobial coatings, such as Cu-PTFE 8% PTFE, silver silicane, Ag-PTFE 4% PTFE and Ni-Cu-P-PTFE were used as model systems with different material properties. Statistical analysis was done using One Way Anova in IBM SSPS.

Bacterial adhesion to antimicrobial coatings increased with increasing material surface energy and elastic modulus. *E. coli* had a much higher adhesion to all antimicrobial coatings compared to *S. aureus*. Adhesion forces increased with an increase in the contact area between asperities. Ag-PTFE 4%PTFE had the highest adhesion forces to antimicrobial coatings. Ni-Cu-p-PTFE had the lowest adhesion forces.

There exist an optimum surface energy for controlling bacterial adhesion at 21-25mJ/m².² Materials can therefore be modified to reduce their surface energy so they do not attract bacteria. *E. coli* is good in forming biofilms and irreversible attachments to materials compared to *S. aureus*.¹ Surface properties of antimicrobial coatings and bacterial strains can be used to predict adhesive forces based on the JKR theory.

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Warm up times of injectable products

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Medicines that are normally kept refrigerated to prevent unwanted microbial growth¹ and slow degradation reactions,² warm up at different rates when outside this controlled environment depending on volume and surface area. Information is required to aid decisions on when to remove medicinal products from a fridge prior to administration,³ or to determine when it is safe to use a product after removal from its controlled environment for a period of time. There is a paucity of information on how long liquids take to warm up during temperature excursions.

0.9% sodium chloride solution was prepared, a range of syringes and infusion bags were filled and placed in the fridge to reduce in temperature. Conditions for the devices were changed to one of three scenarios; left out on a bench, fridge door left open or fridge switched off. Temperature change was monitored via probes and time taken to reach 8°C and 18°C was recorded. Temperature was recorded at different sites within the larger bags. Data was then analysed against surface area to volume ratio to look for trends.

All syringes reached 18°C in less than 30 minutes when left out on a bench, but the 2 ml syringe took over 3.5 hours in a switched off fridge. Bags took longer, 250 ml reached 18°C in just under 1 hour on the bench, and

4 L took nearly 13 hours in the switched off fridge. The general trend seen is that as surface area to volume ratio increases the time taken to warm up decreases.

The relationship is not linear suggesting there are more factors at work than surface area and volume. Smaller volumes increase in temperature at a relatively constant rate throughout the liquid, larger volumes vary in temperature with distance from the surface.

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Design and evaluation of a computer aided package to educate undergraduate and postgraduate pharmacists about the clinical features, prophylaxis and treatment of malaria

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Computer Aided Learning (CAL) is often described as the process by which textual and graphic information is presented in some logical sequence by a computer.^{1,2} The aim of the project was to design and evaluate an animated CAL Package to educate undergraduate and postgraduate pharmacists about Malaria emphasizing the role of the pharmacist.

The CAL package was constructed using Microsoft PowerPoint© and contained relevant up to date information on Malaria.³ Aspects of the package such as the visual appearance, length and interactivity of the package were considered.⁴ Using a 5 point Likert scale⁴ and free text box, a questionnaire was designed to assess the overall impression, presentation/layout and contents of the package.

A total of 30 online questionnaires were completed by Mpharm II students. Nineteen (63%) of the responders were female, eleven (37%) were male yielding a response rate of 29.7%. The mean, mode, frequency and standard deviations were obtained. The majority of students felt the package was well presented. 56% of students (n=17) stated that they would prefer it if CAL packages were used alongside traditional face-to-face transitional methods of teaching. Some students (20%, n=6) preferred traditional methods of teaching as it gave them the opportunity to ask questions. The CAL package was generally well received by the students, and 73% of students would recommend the package to other students as a revision aid, however, they were unlikely to use it solely without supporting lectures themselves.

The malaria CAL package was shown to be a useful reference tool and it can be deduced that the teaching package was successful as an effective learning tool for the students that were involved in the survey. The students who participated in the study found the CAL package interesting, beneficial, and key to understanding the pathogenesis, transmission, and symptoms of malaria.

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The effects of a frankincense extract on breast cancer signalling pathways that control growth and migration

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Natural products represent a rich source of medicinal compounds and have led to the discovery of many drugs we use today. Frankincense has shown to possess compounds that may possess some medicinal properties. The compound BF4 has been isolated from a species of frankincense, *Boswellia frereana*, and investigated

for its use in osteoarthritis.¹ The aim of this study was to understand the mechanism of action of BF4 and explore its potential use as a breast cancer treatment in a triple negative breast cancer cell line, MDA231. The methods used in the study were Western Blotting to identify any changes in proteins that are known to be involved in TNBC cell migration and growth. Immuno-fluorescent microscopy was also used to look at the physical changes of the cells after BF4 treatment.

BF4 was seen to decrease the amount of FAK, SRC and MAP Kinase after 24-hour treatment and at concentrations of 40µg/ml and 80µg/ml. This is shown in an average of densitometry values over three repeated results.

Our data suggests that BF4 can modulate and inhibit the activity of SRC, FAK and MAP kinase, which are known to be involved in aggressive cellular behaviour implicated in TNBC. BF4 can also bring about apoptotic characteristics in the cells, which may result in cell death at higher concentrations and treatment times. As BF4 is a novel compound, more research is required to support these findings before a definitive result can be made.

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What are the opinions of the public of Wales on community pharmacists having access to their hospital discharge advice letter?

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The involvement of a multidisciplinary team in the management of patient's transfer from hospital to community has been shown to improve patient outcomes and reduce re-admissions.¹ Community pharmacy Discharge Medicines Review aims to improve patient compliance and comprehension. NHS Wales Informatics Service (NWIS) are considering whether community pharmacists should be sent a copy of the discharge advice letter (DAL).² However the importance of collecting the views of the public about the community pharmacist's access to their discharge advice letter is key to gain consent for this process to happen. The study aimed to evaluate and quantify the views of the public on community pharmacist's access to the patients' DAL.

A pre-piloted questionnaire³ was sent to a total of 923 participants across Merthyr Tydfil and Ceredigion. This group project used a multi-stage sampling technique to identify clusters based on population size, and then purposively assign categories to local authorities in order to get a representative sample of the whole of Wales. Random sampling using excel was used to select participants from the edited electoral roll. Data was analysed by SPSS 20.

The majority of the public either agreed or strongly agreed with the sharing of their discharge information with the community pharmacist. However 15% (n=86) of participants in Ceredigion and 19% (n=53) in Merthyr Tydfil did not want to share information about drug allergies with the community pharmacist, which may have future clinical implications. The study revealed a low usage of pharmacy services and further education about the role of the pharmacist should help to integrate the services with that of other health professionals.⁴

The results will be fed back to NWIS for review in the hope community pharmacists will gain access to DALs which would be expected to improve patient care and potentially save costs.

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Investigating the role of ZIP7 phosphorylation in breast cancer

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Zinc has long been known to be biologically important in humans, but only recently has it been identified as a second messenger,¹ transferring external stimuli into an intracellular signalling pathway. Zinc cannot travel freely in the body and employs transporters to cross plasma membranes, for example the ZIP7 transporter – which sits on the endoplasmic reticulum and releases zinc into the cytosol from stores when phosphorylated by CK2² at residues Ser275 and Ser276. The project aim was to investigate the importance of residues S275 and S276 individually for ZIP7-mediated zinc release, and to explore the downstream signalling pathways and whether both of these residues were required or whether one alone would suffice.

MCF-7 cells were transfected with recombinant wild-type ZIP7 or a mutated form of ZIP7: S275A/S276A (inactive), S275D/S276A (S275 active) or S275A/S276D (S276 active). They were treated with zinc for 0, 2, 5, 10, 15 and 20 minutes, lysed and analysed by Western blot, and probed for: pAKTS473, pZIP7S275/S276 pCREBS133, p-mTORS2448. Beta-actin was used to normalise the densitometry data. Data was analysed using a one-way ANOVA and a Dunnett's post-hoc test, and significance was assumed if $P < 0.05$.

AKT was confirmed to be activated by ZIP7-mediated zinc release occurring due to the phosphorylation of residues S275 and S276. All results together suggested S276 may be more important for ZIP7-mediated zinc release than S275, but neither residue alone was as effective as the wild-type ZIP7, suggesting the need for both residues for maximal zinc release. For the first time CREB was shown to be activated by ZIP7-mediated zinc release as a direct downstream target.

This project confirmed that a useful target of ZIP7-mediated zinc release (and the downstream proliferative pathways³) for breast cancer treatment should inhibit both S275 and S276.

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Risk aversion in pharmacists

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This study set out to gather information on risk aversion in pharmacists and determine whether pharmacists are risk averse and what tools have been or may be used in the future to measure risk aversion in pharmacists. Very little research has previously been conducted on the personalities of pharmacists and even less has been conducted on risk aversion in pharmacists.

A literature review was performed on a number of scientific databases searching for studies relevant to risk aversion in pharmacists and broadening the search to personality traits of pharmacists. Additionally, any tools used to measure personality found in these studies were themselves part of a parallel search.

The results found no previous studies of risk aversion in pharmacists but nine studies researching pharmacists' personality traits were found. Data relevant to the risk behaviour of pharmacists was extracted from this research and information was also gathered about the tools used in these studies.

The current available literature points towards pharmacists having risk averse personalities. More research needs to be conducted to confirm or refute this finding and there is a need for more UK based research. Some research suggests that risk aversion may have negative effects in pharmacists, for example by hindering their confidence to undertake prescribing roles.¹ This study concludes that, of all the tools used in studies so far, the best suited tool to use for further research into risk aversion in pharmacists is the Gordon Personal Profile Inventory (GPP-I).² Other, more risk-behaviour specific tools, are also suggested as candidates for measuring risk aversion in pharmacists in future research.

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Public opinion of the cost of medicines and strategies to reduce medicines wastage

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Medicines wastage is a considerable problem in the NHS, with approximately £300 million discarded annually, and is a multi-faceted problem requiring complex patient-centred policies.¹ In 2015, the Health Secretary announced plans for a policy that would put the cost of medication on dispensing labels followed by “funded by the UK taxpayer”.² The lack of evidence supporting this policy³ resulted in this study and its aim was to explore public opinion of medicines wastage and potential effects of medication prices on dispensing labels on patient behaviour.

The inclusion criteria were current students, the elderly and working age professionals. Recruitment was conducted via purposive, convenience and snowball sampling. Participants were contacted via gatekeepers and provided with a covering letter and participant information leaflet, detailing what was involved in the study. The focus groups consisted of 5-7 individuals and were facilitated by researchers using a topic guide and labelled medication boxes as props. The discussions were audio recorded, transcribed verbatim and anonymised.

Overall opinion surrounding medicines wastage was that healthcare professionals contributed more than patients. There was an overall negative reaction to the presence of the cost on dispensing labels, with some participants equating it to a “guilt trip”. The majority believed it would have little to no effect long term effect on patient adherence and that policies that engaged the patient more and focused on education would be more effective in curbing medicines wastage due to non-adherence.

This study shows that the public acknowledges medicines wastage as an issue but would not be favourable to the addition of the cost on dispensing labels, preferring a more patient-centred approach. Limitations of this study are the inclusion of professionals allied to the pharmaceutical industry as well as the lack of participants suffering from long term chronic illnesses.

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Evaluation of inhaler technique

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Inhaler devices are used to administer drugs in asthma and COPD. Correct inhaler technique is crucial in delivering drug to the optimal location in the lower airways.¹ Observational studies have shown that inhaler technique in patients is poor² and patients do not understand the need for preventative inhalers.³ The aim was to use airflow measurements to test and classify inhaler technique quality for dry powder inhalers (DPI) and metered dose inhalers (MDI) with and without a spacer device.

Clinics were held across Cardiff and Vale University Health Board (UHB). Information was obtained about patient's inhaler use prior to assessing their inhaler technique using a Vitalograph Aerosol Inhalation Monitor™ (AIM). This records inspiratory flow rate and co-ordination to predict the region of drug deposition. Researchers observed participants to see if they shook the device and held their breath. Participants were also asked if they understood how their regular inhaler helped to improve their condition.

61 participants were recruited who used a total of 88 devices. 26% of all inhaler demonstrations were classed as being good, defined as having drug deposition in the lower airways. DPI technique was better than MDI's

and use of a spacer significantly improved MDI technique ($p < 0.0001$). Previous training, frequency of inhaler use, the use of multiple device types, age and gender did not influence the quality of inhaler technique. 40% of participants did not understand how their regular inhaler therapy helped their condition.

Inhaler technique was poor for all devices; introduction of spacers should improve MDI technique. Current training does not influence technique and evidence suggests that professionals are currently not adequately educated [2]; it is necessary to implement new training tactics and regimes across all healthcare professions, ensuring that patients understand how to use their device properly to maximise the benefits of pharmacotherapy.

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The effects of frankincense extract on breast cancer growth and migration

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Recent research by Cardiff University into *Somalian frankincense*, *Boswellia frereana*, has shown promise as a novel drug candidate for the treatment of inflammatory diseases where it can affect cell proliferation.¹ Currently, little is known as to its potential as an anti-cancer agent. The aims of this project were thus: to investigate the effect of BF4 on the migratory and proliferative capacity of breast cancer cells models reflecting the dominant clinical sub-types.

To carry out this investigation four cell lines were used: MDA-231 (TNBC), MCF-7 (Luminal A), SKBR-3 (HER2+) and BT-474 (Luminal B) cells, with four different concentrations of BF4: 10,20,40 and 80µg/ml. Cellular migration was assessed using a scratch assay where the extent on closure of wounds was measured, whilst a MTT assay was carried out to look at cell viability after treatment. Statistical analysis was carried out using ANOVA followed by a post hoc Tukey's test, showing that there were statistically significant differences between the means in the data sets at $p < 0.05$.

Upon carrying out the assays it was determined that 80µg/ml was the most potent concentration to affect all cell lines in both assays. Cell wounding data indicated a dose dependent inhibition on migration in TNBC cells, with limited effects on the other cell lines. Likewise, MTT assays revealed dose dependent inhibition of growth in TNBC cells again with limited effects on other cell lines.

BF4 may be useful in the treatment of aggressive breast cancers such as those defined as TNBC, either through the inhibition of MMP-9¹ or inducing apoptosis via a number of different mechanisms.^{2,3} Ultimately more research is required in order to determine intricate details as to its mechanism of action upon breast cancer cells.

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Involvement of oestrogen receptor signalling in Alzheimer's disease in women

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Oestrogen is known to be neuroprotective, therefore its post-menopausal loss has been presumed to account for higher incidence of Alzheimer's disease (AD) in women than age-matched men.¹⁻⁴ At least part of ER signalling and thereby some neuroprotection is mediated through its receptors (ERs).^{3,4} The aim of this study was to compare expression levels of ERs and other AD-associated proteins in AD and non-AD (control) samples of both genders.

Western blotting analysis determined levels of both ER subtypes (ER α & ER β) along with an ER signalling protein (GSK3 α/β) and AD hallmark pathological proteins (amyloid precursor protein, APP and total & phosphorylated tau) in human brain cortex samples. Comparisons were made across both disease status and gender.

Levels of ER α & ER β were significantly increased in AD-women compared to control-women whereas in AD-men there was a significant decrease of ER β compared to control-men. Additionally, levels of ER β were significantly lower in AD-men compared to AD-women, whereas in control-men levels of ER α were significantly higher compared to control-women. Levels of APP (as expected), phosphorylated and total tau & GSK3 (α/β) showed no differences between men and women with AD. However, in control-women GSK3 β expression was significantly increased compared to control-men.

Overall, this study indicates that there are differences in ER expression with regard to both gender and disease status. The data suggest that differential expression levels of ER and some ER signalling molecules may affect the extent of neuroprotection, which may explain gender-based differences of prevalence. However, future investigations are needed to support these findings and ascertain if ER signalling-mediated changes could be considered as a prominent risk factor to develop AD. If conclusive evidence is achieved it could be a valid basis for its investigation as a potential target for future AD therapies.

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Spore adhesion of purified 002 and 027 ribotype *C. difficile* spores to stainless steel surfaces

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Clostridium difficile is an anerobic, gram-positive, spore-forming bacterium. Hospitalized patients treated with broad-spectrum antibiotics are more susceptible to *C. difficile* infection (CDI) due to alterations in their colonic microbiota. Sporulation of *C. difficile* is induced by environmental stresses e.g environmental oxygen. The spores may survive for months on inanimate surfaces found throughout healthcare environments, one of these being stainless steel. Once the spores are ingested, they germinate in the small intestine and release toxins that can cause bloody diarrhea and colonic ulceration.

During the past decade, CDI rates have been increasing worldwide, this is largely thought to be due to a 'hypervirulent' ribotype of *C. difficile*, 027. Previous studies have suggested that strains that possess the 027 ribotype produce spores that have greater relative hydrophobicities, possibly aiding them to adhere to stainless steel more strongly. The aim of this study is to compare the adherence of purified 027 strain spores (1801,1813) to stainless steel against that of the less virulent purified 002 strain spores (1748).

Three spore suspensions were created for each strain to be investigated and their concentrations of colony forming units per ml recorded. 10 μ l from these spore stocks were further cultivated on the appropriate agar or in the appropriate broth and were subjected to two separate purification methods. The Lawley method produced spores of higher purity than the Sorg, but the reagents used in the Lawley method possibly disrupt the spore exosporia, altering the spores' ability to adhere to stainless steel.

The stainless steel transfer assay was used to determine the spore samples adherence to stainless steel. The one-way ANOVA found no significant differences between the adherences for the unpurified, Sorg and Lawley 1801 strain spore samples. Unpaired students t-test was used to compare adherence of the different strain spores to stainless steel against each other. The only significant result obtained was that the Sorg 1813 spore samples adhered less strongly to stainless steel.

By gathering more information regarding how and to what extent the spores adhere to inanimate surfaces found throughout healthcare settings, CDI rates may be able to be combated more efficiently.

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Development of a molecularly imprinted polymer sensor for detection of PSA

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Successful treatment of Prostate cancer (PCa) relies on early diagnosis (detection of elevated prostate specific antigen (PSA) levels). Currently this process can take several weeks.¹ The aim was to develop a highly selective biochemical sensor for the detection of PSA using molecular imprinting to allow rapid detection, diagnosis and monitoring of PCa within a primary care setting.

Epitope imprinting was adopted due to the issues associated with protein imprinting.^{2,3} An epitope sequence of PSA was synthesised following solid phase Fmoc synthesis on a 0.3 mmol scale. It was then immobilised to ED-SE1-AuPt electrodes with the use of aminothiophenol (ATP) and 3, 3'-dithiobis (sulfosuccinimidyl propionate) (DTSSP). Electropolymerisation of dopamine or aminophenol onto the peptide modified electrodes took place to create molecularly imprinted polymers (MIPs). Electrical impedance spectroscopy (EIS) was then used to detect possible rebinding interactions with the MIP and the peptide.

High performance liquid chromatography (HPLC) and mass spectrometry (MS) confirmed the synthesised peptide was both pure and matched the desired sequence. Dopamine MIP displayed increased rebinding in comparison to polydopamine alone. However, when compared to a dopamine non imprinted polymer (NIP) it was evident that a specific imprinting effect had not been achieved. Non-specific binding was observed with polyaminophenol at low concentrations (>10 µM). Similarly to polydopamine, there was little to differentiate between polyaminophenol MIP and NIP.

It is evident from the results that an imprinting effect could not be established on this occasion. This could be due to a number of reasons including lack of imprinting to the length of the peptide or overcrowding at the electrode surface, resulting in non-specific binding sites due to polymer porosity. Future work should include extra polymerisation cycles and decreased concentrations of molecules on the surface of the electrodes in the hope to overcome these issues.

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Determining intravenous lipid emulsion stability – an examination of sensitivity of analytical methods

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Parenteral lipid emulsions are used clinically as nutritional supplements.¹ Emulsifiers are used in emulsions to stop or slow down the separation of an emulsion into its original state, therefore keeping the emulsion stable.² When an emulsion becomes unstable the lipid globules flocculate, causing a cream layer to be formed and then eventually they coalesce causing cracking of the emulsion, which is irreversible.³ It is important that an emulsion is stable when given to a patient as globules greater than 5µm can harm patients. This is why the limit of 5µm has been set to determine if an emulsion is stable or not.² This stability testing is essential for patient safety, so that when patients receive parenteral lipid emulsions in clinical practice they are not harmed by unstable emulsions containing large globules.⁴

To test the emulsions stability calcium chloride was added in different concentrations to Intralipid® 20% and SMOFlipid® 20% to destabilise them. Their stability was then tested using three different techniques. Visual inspection looked for signs of creaming and cracking. Microscopy measured the size of individual globules and looked for signs of aggregation and flocculation. Laser diffraction was used to measure the maximum size and mean volume weighted diameter of globules.

Intralipid® had the most destabilisation at 6mmol/L of calcium chloride and SMOFlipid® had a wider range of concentrations that showed destabilisation, which was between 4 and 8mmol/L of calcium chloride. The difference in stability between the emulsions is likely due to the different composition of their lipid phases.

The project has limitations, namely it does not answer the second part of the research question, how sensitive are the analytical methods. This was due to time constraints. The project does provide a good base for future work and is important in keeping patients safe from adverse affects of unstable emulsions.⁴

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Comparing tau phosphorylation in mouse models of Alzheimer's disease and Down's Syndrome

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The Alzheimer's disease pathophysiological hallmarks are Amyloid- β ($A\beta$) inclusions and neurofibrillary tangles containing tau.¹ Amyloid precursor protein (APP) becomes cleaved to create $A\beta$. Increasing $A\beta$ levels upregulates kinases such as DYRK1A, phosphorylating tau at Thr212, and GSK-3, phosphorylating tau at Ser396/404. Here three 10 month-old mouse models and wild-type control mice were used. The Tg2576 mouse overexpresses human APP. Down's syndrome (DS) subjects have three copies of human chromosome 21 (Hsa21), encoding APP and DYRK1A. Tc1 mice are partially trisomic for Hsa21 excluding the APP encoding region. The Doubles mouse contains the mutations from both Tg2576 and Tc1 mice, reintroducing APP into the Tc1 model. I hypothesise Doubles mice will have higher kinase and phosphorylated tau protein levels than all other groups.

Western blotting technique was used to analyse the protein expression of APP, DYRK1A and Thr212, GSK-3 and Ser396/404 in cortex samples from all mice. Data were analysed with one-way ANOVA and Tukey post-hoc test.

Results showed increased APP levels in Tg2576 and Doubles compared to Tc1 and wild type. No significant differences were seen between DYRK1A, GSK-3 α and GSK-3 β and their associated phosphorylated tau residues between any of the groups.

The expected increases in DYRK1A and Thr212 levels were not seen in Doubles and Tc1 mice. The Tc1 mouse exhibits mosaicism,² causing sporadic gene uptake and affecting results. The genes on Hsa21 are present on mouse chromosomes 10, 16 and 17.³ Therefore manipulation of Hsa21 in Tc1 mice will not cause DS. The expected increases in GSK-3 and Ser396/404 levels in Tg2576 and Doubles mice were also not seen, possibly as they were too young to have phosphorylated tau widespread in the cortex.⁴ DYRK1A and GSK-3 were unaffected by increasing levels of APP in the Doubles mice, however, recent improved DS models will facilitate analysis of this hypothesis.

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Design and synthesis of inhibitors of CYP24A1 as potential cancer therapeutics

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Calcitriol, the active metabolite of vitamin D, can be potentially used as an anticancer agent due to its antiproliferative, pro-apoptotic and antiangiogenic activities.¹ However, this therapy still remains a challenge due to hypercalcaemia caused when used in high dose.² CYP24A1, the enzyme for metabolising and inactivating calcitriol, is thus explored as inhibiting this target can increase the body's endogenous level of calcitriol. CYP24A1 inhibitors can also tackle drug resistance to calcitriol caused by the up-regulation of CYP24A1 found in cancer patients.¹ The aim of this project is to design and synthesise CYP24A1 inhibitors and obtain compounds for establishing structure-activity relationships of *N*-(2-(1*H*-imidazol-1-yl)-2-phenylethyl)-4-benzamides derived from the lead compound, VID-400.

Through molecular modeling, the *p*-substituents of benzamide of the proposed inhibitors were modified for better docking with the CYP24A1 homology model. The final compounds, imidazole-benzamides, were then synthesised with a three-step reaction method. All compounds including the intermediates were characterised to confirm their purities before proceeding to the next step.

All six computer models of the (*R*)- and (*S*)-imidazole-benzamides could bind to the haem Fe of the enzyme in optimal distances (2.04-2.25Å) by a N-Fe interaction and interact with hydrophobic amino acids. The reaction scheme successfully produced two pure imidazole-benzamides in low yields (~7%).

The proposed inhibitors show promising modelling results due to the essential N-Fe interaction at optimal distance found in all computer models, as well as the hydrophobic interactions that are also present between calcitriol and CYP24A1. However, their actual inhibitory effects have to be evaluated in cell-based assays and these results are not yet available. The reaction method produced pure imidazole-benzamides, except when the benzamide was the *p*-methoxylated benzene because the strong electron-donating OCH₃ was unfavourable in the syntheses of imidazole and the oxazoline intermediate.

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Feasibility of using an iPad to assess patient measures in a movement disorder clinic among Parkinson's disease patient cohort

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Integration of electronic devices into healthcare services is becoming more common.¹ This study aims to evaluate the feasibility of using an iPad to assess patient measures as part of routine in a movement disorder clinic (MDC), particularly for Parkinson's disease (PD) patients. The main objectives are to explore patient's and staff's perspectives towards the integration and to find out what support is required for this to run routinely.

Ethics approval was granted and the study was carried out as a service evaluation. All PD patients were invited to complete an iPad activity that would record their health status via EQ-5D,² non-motor symptoms (NMS) via the electronic NMS questionnaire³ and speed with the simple finger-tapping task. A short semi-structured interview was later conducted by students to evaluate the service. Staff members in the clinic are also interviewed.

Of 24 patients participated, 67% were able to use the iPads on their own. Some patients still required help from others, but they usually come in with their carers. Majority of patients felt comfortable and preferred the electronic approach over paper-based questionnaire after trying the iPad. There was no issue for PD patients to complete the iPad activity in time.

Patients and staff were open to the idea of implementation. Staff were more concerned about the extra workload they might be having. The reliability of this study was limited by the small cohort size (n=24) and short study period. The approach outlined in this study should be replicated with other MDCs to see if there is any shortcomings. In conclusion, the use of iPads is acceptable by PD patients and is feasible in a MDC given

that sufficient assistance is readily provided to patients, in helping them to use or to complete the iPad activity.

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Evaluation of CHST11 and HES1 gene expression in endocrine resistant breast cancer

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Breast cancers can express oestrogen receptor (ER+), accounting for 70%,¹ while others are ER-. ER+ disease comprises luminal A and B sub-types. Anti-hormones are the most important therapy for all ER+ patients, but effectiveness is limited due to acquired resistance.² 11 new long-term endocrine-treated cell lines have been developed from luminal A (MCF7, T47D) and luminal B cells (BT474, MDA361) to investigate resistance. Affymetrix microarrays discovered up-regulated CHST11 and HES1 in some luminal A-derived lines. To investigate whether these genes might contribute to resistance, the aims of this study were to verify the Affymetrix profile in the MCF7-derived cells and extend study to other luminal A and B-derived models, to examine if there is any link with ER, and evaluate gene ontology and clinical profile.

RT-PCR determined expression of CHST11, HES1 and ER in luminal A (MCF7, T47D) and luminal B (BT474, MDAMB361)-derived resistant models versus controls. KMPLOTTER related gene expression level with clinical tamoxifen outcome using publicly-available datasets. Ontological information was obtained using PubMed and Genecard.

CHST11 expression was induced only in MCF7-derived and T47D-derived resistant models. In contrast, HES1 increased in luminal A and luminal B-derived resistant models. No relationship was found between induced expression and ER. Clinical profiling showed high intrinsic expression of CHST11 (luminal A) and HES1 (luminal A and B) associated with shorter relapse-free survival in ER+ tamoxifen-treated patients. Ontological research showed increased CHST11 (involved in synthesis of chondroitin sulphate) and HES1 (effector of Notch signalling) play a role in cancer growth, progression³ or drug resistance.⁴

These experimental and clinical data showed there might be a contribution for increased CHST11 in luminal A-derived resistance and for HES1 in all endocrine resistant states. Further studies to explore the role in driving resistance are warranted to determine whether their pathways have targeting potential.

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Is there a role for a veterinary pharmacist in the management of dairy mastitis?

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Dairy mastitis is inflammation of the mammary gland (udder tissue) in response to bacterial infection.¹ Mastitis is the largest dairy health problem in the UK,² causing reduced milk yield and quality.³ Veterinary pharmacists can support farmers treating mastitis, encouraging prudent use of antibiotics. This study aims to explore factors influencing dairy mastitis incidence, understand rationale behind antibiotic treatment and explore requirements for veterinary pharmacists to educate farmers.

A semi-structured interview was undertaken with a representative sample of 18 dairy farmers. Qualitative questions looked at causative factors, diagnosis and treatments. Quantitative data for monthly mastitis cases

was collected and analysed using GraphPad Prism. A one-way ANOVA with Tukey's post hoc test compared mastitis rates between farms. A t-test determined the significance of farm mastitis rates against the overall mean. Differences in individual farm mastitis rates were attributed to variations in farming practices. Ethics approval was obtained.

Mastitis rates varied significantly between farms but no clear correlation was seen with farming practices. The quality of staff and harsh culling policies had major impacts on mastitis incidence. Standard Operating Procedures for the use of antibiotics were exhibited by 79% of farms. Furthermore, 21% of farmers weren't aware of antibiotic resistance. Current treatments hadn't been changed for over 24 months at 63% of farms, indicating emergence of resistant bacterial strains. One farm used a veterinary pharmacist and only 16% knew what one was.

Veterinary pharmacists aren't currently playing an active role in dairy mastitis. Limited advice means farmers adopt a 'trial and error' approach to reduce mastitis incidence. Antibiotics are routinely supplied to farmers with little instruction on appropriate usage protocols. Education is key to preventing emergence of resistant bacterial strains. There is clearly scope for a veterinary pharmacist to work alongside veterinarians in the management of dairy mastitis.

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The relationship between endocytosis and wnt signaling in Alzheimer's disease

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Alzheimer's disease (AD) an age-related, neurodegenerative disease has two hall mark pathological features, amyloid- β ($A\beta$) plaques and neurofibrillary tangles.¹ The amyloid cascade hypothesis suggests that the buildup of $A\beta$ is the pathological cause of AD. $A\beta$ is formed from the processing of the amyloid precursor protein (APP) by β - and γ -secretase in early endosomes.² Both endocytosis and Wnt signaling dysfunction have been observed in AD pathophysiology.^{2,3} This study examined clathrin-mediated-endocytosis (CME) and clathrin-independent-endocytosis (CIE) in order to study the effects these have on the Wnt signaling pathway.

siRNA targeting endocytic-related proteins, clathrin and PICALM (CME), and caveolin-1 (CIE) were transfected into neuroglioma cells. Culture media and siRNA targeting non-coding green fluorescent protein (GFP) were used as negative controls. Once sufficient endocytic-related protein knockdown was achieved, levels of key Wnt-related proteins, beta catenin (total and non-phosphorylated), GSK 3 α , GSK 3 β , TCF7L2 and LEF 1 were examined by Western blotting. All data were expressed relative to untreated control values after normalisation to GAPDH.

Statistically significant knockdown of the CME and CIE related proteins was achieved. Levels of non-phosphorylated beta catenin were statistically significantly increased following treatment with siRNA targeting clathrin. Levels of GSK 3 β were significantly decreased following treatment with siRNA targeting caveolin-1.

Previous studies have shown that silencing these endocytic-related proteins inhibits the relevant endocytic pathway. Inhibition of CME, specifically via clathrin, leads to an increase in non-phosphorylated beta catenin the key effector of the Wnt pathway and inhibition of CIE leads to a decrease of the Wnt inhibitory mediator GSK 3 β which both imply an upregulation of the Wnt pathway.³ This suggests that endocytosis may suppress the Wnt pathway and potentially by endocytic internalization of receptors.⁴ However further studies are required to better understand this complex relationship and how exactly endocytosis mediates Wnt signaling.

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Does copper ibuprofenate have potential to be a new topical treatment for arthritis?

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Arthritis is a disease related to the inflammation of joints and there is no cure to date. However, non-steroidal anti-inflammatory drugs (NSAIDs) are given as first line treatment. Copper has long been associated with arthritis due to its anti-inflammatory properties and the synergistic activity of copper with drugs such as NSAIDs.¹ Cu-NSAIDs have been synthesized and investigated^{2,3} but not investigated for topical delivery. This study aimed to: (i) determine the association constant (K_a) of ibuprofen and diclofenac metal ion complexes, (ii) determine whether topically applied copper ibuprofenate can deliver both ibuprofen and copper(II) simultaneously across the skin.

The Benesi-Hildebrand (BH) equation was used to determine the K_a of metal-NSAIDs from UV spectrophotometry results. Copper ibuprofenate was prepared and an ethanolic solution formulated; equimolar ibuprofen in ethanol served as control. Porcine skin was prepared as native and tape-stripped membranes. In-vitro permeation studies were carried out using Franz diffusion cells by dosing the skin for 6, 20 and 48 hours. The receptor phase was analysed using HPLC and UV spectrophotometry for ibuprofen and copper(II) permeation respectively.

The K_a for Cu(II)-diclofenac and Cu(II)-ibuprofen were 26.46M^{-1} and 196.46M^{-1} respectively. Cu(II)-ibuprofen was prepared as copper ibuprofenate and used in skin permeation experiments. Ibuprofen and copper(II) permeation increased with time, slightly greater ibuprofen permeation was observed across tape-stripped skin compared to native, although $p > 0.05$. Similar results found for copper(II) permeation across tape-stripped skin and native using copper ibuprofenate, except for at 6 hours. Ibuprofen control treated on native showed similar results as copper ibuprofenate treated on tape-stripped skin ($p > 0.05$).

This study showed that the association constant of metal-NSAID could be obtained using the BH equation. Topically applied copper ibuprofenate can deliver ibuprofen and copper(II) simultaneously across skin. Overall, the data support the further development of this complex as a potential new topical delivery system for arthritis.

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Development and manufacture of high strength loperamide capsules

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This project was developed in response to Saint Mary's Pharmaceutical Unit in Cardiff & Vale University Health Board receiving requests from clinicians for a high strength capsule formulation of loperamide. Commercially, the only loperamide capsule formulation available is a 2mg capsule, therefore, an 8mg capsule formulation was proposed. This high dose formulation will be used to treat stoma patients who are routinely prescribed large doses, and with fewer capsules to achieve the therapeutic dose, there will be improved patient convenience and compliance.

Three excipients (lactose monohydrate 100M, maize starch and microcrystalline cellulose) were studied with loperamide hydrochloride for their flow, filling and mixing properties and three potential formulations were developed. Bulk powder was produced by mixing individually weighed ingredients in a pestle and mortar, followed by multiple inversions in a sealed plastic bag. Capsules were filled using a size 2 ProFill encapsulator at SMPU under Good Manufacturing Practice (GMP) conditions. Samples were taken from the bulk mix and manufactured capsules for analyses. A High Pressure Liquid Chromatography (HPLC) method was developed and validated for accurate loperamide quantification.

The results showed that one of the three formulations, containing lactose monohydrate 100M and maize starch met the bulk mix and capsule content specification of $\pm 5\%$ of the expected loperamide content.

This lead formulation warrants scale up to a batch size of 1000 capsules, provided manufactured capsules meet the dissolution test specification. Further analyses are required to confirm the suitability of the manufacturing process to produce a homogenous bulk mix and uniformly filled capsules. Saint Mary's Pharmaceutical Unit has confirmed that this formulation will be further developed as a new unlicensed product.

Evaluation of patient's inhaler technique in the Cardiff and Vale University Health Board

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Observational studies have confirmed that one of the key reasons behind poor asthma and COPD control is due to poor inhaler technique,¹ leading to minimal deposition of the medication in the smaller airways of the lungs, diminishing the therapeutic effect.^{2,3} Therefore, we conducted a study to identify and quantify patient's inhaler technique through the use of a Vitalograph Aerosol Inhalation monitor device.⁴

Patients were recruited from GP asthma/COPD clinics, hospitals as well as the Student's Union of Cardiff University. After a short initial questionnaire, the patient's inhaler technique using a dummy Dry powder inhaler and /or meter dose inhaler with or without a volumetric spacer was assessed and recorded using the Aim device. The quantitative data produced was analysed by chi-squared test, in which statistical significance was taken at $P < 0.05$. The total number of study patients was $n=61$.

The results of the study indicated that 83% of the patients failed the inhaler technique test whilst on a MDI. However patients were significantly better with volumetric spacers used with MDIs, in which only 9% of the patients attained a "fail" technique. The Technique for DPIs was significantly better than MDIs (P -value < 0.0001) although 50% of DPI users fell under the suboptimal category as they failed to generate sufficient inspiratory airflow. Majority of the patients reported nurses as the last healthcare professional to give them guidance on inhaler technique (75%); however 78% of these patients attained a fail technique.

The results clearly illustrate that patients had a poor inhaler technique in the Cardiff and Vale University Health Board particularly for MDIs. However with the spacer device they were significantly better. The study is conducted in a limited geographical area; therefore future work needs to be conducted through expansion to other areas in the UK through collaborations with other health boards.

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The public's opinion on pharmacists having access to patients' hospital discharge advice letters

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Prior to patients being discharged from hospital, a discharge advice letter (DAL) is produced stating the reason for admission, diagnosis, medication changes and follow up instructions.¹ A copy is sent to the patients' GP following discharge and a summary is provided to the patient. It is not sent to the patients' regular community pharmacy. The aim of this research project was to gather the public's opinion on community pharmacists having a copy of the patients' DALs. It investigated what information they were happy to share and by what method. The project was conducted as a group across Wales in which each member of the group ($n=4$) was assigned a specific area. This particular project focused on Ewloe, Flintshire.

A pre-designed piloted questionnaire was used to gather the public's opinion.² A total of 893 questionnaires were sent out to Ewloe. Questionnaires, cover letters and pre-paid returned envelopes were sent out on 2nd November and a two-week deadline was given. Returned questionnaires were inputted and analysed using SPSS version 23.

A total of 118 usable questionnaires were returned, giving a response rate of 13.3%. The vast majority of the respondents were happy to share their hospital DAL with their community pharmacy. Almost 65% of the respondents felt that it would be useful for the pharmacist to receive a copy of their DAL. 'Allergies' was the most preferred information respondents were happy to share with around 30% either 'agreeing' or 'strongly agreeing.' The method respondents preferred to transfer the information could not be clearly identified.

All the group findings now need to be combined together to see the overall trend throughout Wales. This will help to decide whether or not community pharmacists should have access to patients' DALs. As this project was conducted in Wales, no generalisation can be made across the UK.

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Investigating the role of ZIP7 phosphorylation in breast cancer: the importance of S275 and S276

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ZIP7 is a zinc transporter found on the endoplasmic reticulum membrane,¹ known to be upregulated in tamoxifen resistant breast cancer cells,² responsible for the release of zinc from intracellular stores as a "zinc wave". ZIP7 mediated zinc release activates multiple downstream pathways via protein tyrosine phosphatase inhibition which leads to processes such as cell proliferation and migration involved in cancer growth.³ Previous research has found that ZIP7 activation is dependent on phosphorylation of the channel by CK2 at two specific serine residues, S275 and S276.⁴ This study looked at the differential importance of the individual residues for ZIP7 phosphorylation and activation of downstream pathways involving AKT and GSK-3 β .

Cells transfected with; wild-type ZIP7 (S275/S276), S275A/S276A (null-mutant), S275D/S276A (active S275 residue) or S275A/S276D (active S276 residue) were treated with zinc for 0, 2, 5, 10, 15 or 20 minutes. Samples were probed with pZIP7, pAKT and pGSK-3 β antibodies by Western Blot Analysis.

The results confirmed previous findings that AKT and GSK-3 β are phosphorylated downstream of ZIP7 mediated zinc release.⁴ Data suggests that GSK-3 β is phosphorylated directly by zinc. ZIP7 phosphorylation is possible with only one functioning residue, however downstream activation of AKT is decreased in S275D/S276A and S275A/S276D mutants compared to wild-type, suggesting both residues must be phosphorylated to activate AKT. Results suggest that residue S276 is not required for, and may interfere with, downstream GSK-3 β inhibition, suggesting that phosphorylation at S275 is responsible for downstream GSK-3 β inhibition.

Lack of statistical significance means no solid conclusion can be drawn as to whether S275 and S276 residues have different impacts on ZIP7 phosphorylation and AKT activation. However, if as the results suggest, S275 is more significant for GSK-3 β inhibition downstream of ZIP7, this would indicate a more specific biomarker or possible therapeutic target with regards to ZIP7 mediated upregulation of certain cancer pathways.

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Can Welsh plants yield potential compounds for the treatment of glioma?

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The aim of the study was looking at whether plants cultivated in Wales are able to provide new treatments for glioma. Techniques used for purification were ethyl acetate extraction and chromatographic techniques. These

included preparative TLC and size exclusion column chromatography using sephadex LH-20. Results were analysed using a combination of analytical TLC and mass spectrometry. LLAMA (Lead likeness and molecular analysis) was used to investigate the modification of isolated compounds and assess how 'drug-like' its derivatives can be. From that, a semi-synthesis was run in an attempt create an isopropyl derivative.

This study found reasonable quantities of lead compounds in both plant extracts. High levels of plastic impurities were discovered in the samples, which was due to the storage of the extracts. The mass spectrometry analysis identified known compounds alongside a whole range of unidentified masses. These could well be unidentified compounds that may have therapeutic promise. The semi-synthesis was unsuccessful but this was probably due to the fact that only one attempt was made.

The plants studied have shown good potential to yield lead compounds for future research and this should be continued to be explored.

Evaluation of medicines administration and errors associated with the use of antidepressants in care homes

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There is a high prevalence of antidepressant use by residents in care homes, with the likelihood that their use is associated with significant medication administration errors.^{1,2} The aim of this study was to determine the extent of antidepressant use, and to identify the nature and frequency of associated medication errors incurred as a result of prescriber and administration errors in the care homes.

This was a retrospective study of residents' electronic medication administration records (eMAR) from care homes located in South Wales. The findings reported represent only a 3-month period. The eMAR database was investigated against error types that had been decided through a pilot study and group consensus prior to conducting the full analysis. These error types, either made by the prescriber or the care home, were; 'Dose', 'Drug Choice', 'Duration' and 'Frequency' and were further divided into sub-categories. Results were tabulated or graphed accordingly and analysed statistically.

A total of 84 residents and 6201 administrations from 11 care homes had been analysed which resulted in 28.7% of residents on different antidepressants. There was a total of 4 out of 84 Prescriber Errors; 3 Dose and 1 Drug Choice, which resulted in an incident rate of 4.76%. The Care Home Errors were a total of 1761 out of 6201 with an incident rate of 28.4%. 77% of the Care Home Errors were due to Frequency Errors and 23% due to Dose Errors. The Pearson Correlation statistical test revealed a positive correlation between the Total number of Administrations per Care Home and the Total Number of Antidepressant Errors per Care Home.³

The study reveals that medication management is still a challenge, more so for care homes.^{2,4} Further research is needed to determine the root cause of these errors in care homes and ensure a more effective system is adopted.

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The evaluation of anti-infective medicines management and associated errors in Care Homes

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Care Homes accommodate some of the most vulnerable residents that often have multiple health problems, putting them at high risk of medication errors.¹ The aim of the present study is to identify the prevalence and

types of prescribing and administration errors relating to anti-infective agents in Care Homes and to quantify the extent of anti-infective prescribing.

A retrospective study was conducted in 12 Care Homes in South Wales over an eight month period (Feb-Oct). Anonymised real-time data was collected from an electronic medicines management system. A total of 142 residents on anti-infectives were identified and 9499 administrations were analysed against pre-defined medication error categories. These errors were broadly classified into Care Home Administration errors and Prescribing errors. Within both categories, a set of sub-categories were further identified. The type and frequency of medication errors were recorded in Excel and selected data was transferred into SPSS for further analysis.

A total of 2247 medication errors were recorded for the 142 residents; 79.6% of residents were exposed to at least one error. The most frequent administration error types were 'duration' errors (44.5%), followed by 'omission' errors (38.9%). Similarly the most common prescribing error type was 'duration' errors (74.3%) for a shortened period of time (65.7%). Out of 329 residents, 142 (43.16%) were prescribed one or more anti-infective agents during the eight-month sampling period. The most frequently prescribed was Trimethoprim, which accounted for nearly one quarter (24.6%) of all anti-infective prescriptions.

The evaluation of the management of anti-infectives in Care Homes in South Wales reveals that the incidence of administration and prescribing errors is high. Future work should include a clinical impact assessment to determine the severity of these errors and root cause analysis to understand why these errors are occurring to aid in the development of preventative strategies.

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Formulation factors affecting the precipitation of selenium in parenteral nutrition admixtures

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Selenium is a trace element used in parenteral nutrition admixtures. Selenium acts as a component of glutathione peroxidase which is an important antioxidant.¹ Little is known about the stability of selenium in parenteral nutrition other than that ascorbic acid can act as a reducing agent, reducing it to elemental selenium, this effect being henced by copper.² Due to their buffering action amino acids can prevent this reduction suggesting that pH plays a role in the stability of selenium.³

31 batches of test admixtures were prepared, containing amino acids, glucose at 20 and 70%, ascorbic acid and copper, whilst some were buffered to pH 3, 7 and 9. All were observed and tested at time points 0, 24, 48 and 72 hours. There were three samples in each batch. Controls were made for each batch with the components being tested but without the selenium to determine if selenium was the cause of any precipitation found in the study. All admixtures were prepared aseptically in a laminar flow unit to minimise any contamination. Visual inspection using fibre optic lights was used to determine if any precipitation was present and the extent. A Hach turbidimeter was used to give an accurate value of turbidity, whilst an Orion pH meter was used to record the pH of the admixtures.

No visible signs of precipitation were observed in any of the test batches. All test batches containing selenium with ascorbic acid and copper, one sample from the batch of selenium with ascorbic acid at acidic pH and all samples from the batch of selenium with ascorbic acid at neutral pH had a change in turbidity >0.5 suggesting possible precipitation was undergoing, however there was also a >0.5 change in NTU in the control batches suggesting that this change wasn't necessarily due to the selenium.

The results showed that selenium is generally stable when mixed with a wide range of parenteral nutrition components and stored for a period of three days.

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An evaluation of the management of dementia & Parkinson's disease medication in care homes

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There is evidence to suggest that medicines management within care homes is a problem.¹ This study aims to evaluate the prescribing and administration of dementia and Parkinson's Disease medication in a sample of care homes in Wales.

A literature review was conducted to find clinical guidance. Error categories were defined broadly as either prescribing or care home errors and then further subcategorised. The data to be analysed was then collected from an electronic medicines management system. Prescribing rates of Dementia and Parkinson's Disease medication were extracted and all 6052 administrations were analysed individually to identify and record both prescribing and care home errors. SPSS was used to apply the Pearson correlation co-efficient test to identify if there was a correlation between the total administrations for all drugs (per care home) and the total care home errors for Dementia and Parkinson's Disease medication (per care home).

47 of 52 patients encountered errors and 31.3% of administrations had an error. In terms of prescribing, there were only dosing errors, which affected 7 patients. In care home errors, dose and frequency errors occurred. Frequency attendant errors, where the drug was given over 2 hours early or late, were most prevalent and affected 17.2% of administrations. On average, for every 4 administrations there was a care home error. A significant positive relationship existed between total administrations and the total Dementia and Parkinson's Disease errors in a care home, however caution has to be taken with this as there was an outlier affecting the results.

A high number of care home errors indicate that medicines management in care homes is challenging. Further work is needed to undertake a root cause analysis to establish why these errors are occurring, how they can be resolved and to ensure that patient safety is not being compromised.

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Depression in Lewy body diseases

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Parkinson's disease dementia (PDD), Lewy body dementia (LBD) and Parkinson's disease (PD) are all classed as Lewy body diseases and are associated with both motor and non-motor symptoms. The four cardinal motor symptoms include bradykinesia, rigidity, postural instability and a resting tremor.^{1,2} Non-motor symptoms can include dementia and depression, which can significantly reduce the quality of life in these patients.³ Polypharmacy (use of four or more drugs simultaneously) can be an indication of comorbidities. It is linked to chronic diseases such as PDD, LBD and PD and could be a cause of depression in these patients.⁴ The aim of this research is to determine whether there is a link between polypharmacy, depression and the three Lewy body diseases.

A retrospective study was carried out using "The Electronic Clinical Network Parkinson Disease and Related Disorders Database", which contained information on PDD, LBD and PD patients. Demographics and incidence rates were compared. Depression, polypharmacy and Levodopa equivalence (LED) (a measure of drug equivalence) were all studied and compared between the diseases and related to their depression classification.

Out of a total of 1033 patients, 71.64% had PD and 28.36% had either PDD or LBD, with a higher proportion of males in each disease. Levels of polypharmacy were significantly higher in patients with PDD than PD. Within PDD and PD levels were higher amongst patients taking antidepressants than in depressed patients not taking antidepressants or non-depressed patients. Significant differences were seen in LED between PDD, LBD and PD patients. Within PD, patients who showed signs of depression (whether on antidepressants or not) had a significantly higher LED compared to patients who were not depressed.

There is a strong relationship LED and depression in PD patients. However polypharmacy is linked closely to whether a patient is being treated with antidepressants or not.

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Design and synthesis of novel mycobacterial CYP121 inhibitors as potential tuberculosis inhibitors

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Tuberculosis (TB) is an infectious, bacterial disease caused by *Mycobacterium tuberculosis*. Despite an estimated 47% mortality reduction (1990-2014), TB caused 1.5 million deaths in 2014, partly due to the emergence of multi-/extremely-drug resistant (M/XDR) bacterial strains.¹ The currently recommended treatments, isoniazid, rifampicin, ethambutol and pyrazinamide, present other issues relating to toxicity, drug-drug interactions and duration of treatment.² Considering this, there is an increasing need to develop either novel TB agents or to repurpose existing agents. The bacterium's genome encodes for 20 cytochrome-P450 (CYP) enzymes, one in particular, CYP121, is essential and specific.³ The aim of this project was to design and synthesise at least one compound that could inhibit this intriguing target and become a TB therapeutic of the future.

Molecular Operating Environment software was used initially to understand how cYY (the natural substrate), fluconazole (a high affinity ligand) and a series of four compounds (F, G, H and I) bind within the CYP121 active site. Compounds F and G were synthesised via a four step reaction scheme starting with 3-acetylpyridine (compounds H and I were not made successfully due to a failed chlorination step).

Theoretical computer models showed that compounds G, H and I could form a direct haem interaction in the CYP121 active site, and suggested that compound F would bind indirectly via water (similarly to cYY [3]). Phe-168, Gln-385 and Arg-386 were identified as key binding residues. ¹H/¹³C-NMR were used to confirm the identity of compounds F and G, and despite low recrystallised yields (46% and 25% respectively) both compounds passed microanalysis.

If activity is observed in further assays against CYP121 and *M. tuberculosis*, the favourable drug-like properties (according to Lipinski's 'Rule of Five'),⁴ the relative ease of synthesis and the potentially novel mechanism of action suggests great potential for compounds F and G.

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The public's opinion on community pharmacists (chemists) having access to patients' hospital discharge information

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A Discharge Advice Letter (DAL) from hospital contains information on medication changes and diagnoses. This is currently sent from hospitals to a patient's GP surgery, but not community pharmacies, after discharge. Research shows that 85% of the British public said that they wanted any healthcare professional treating them to have secure electronic access to key data from the GP record.¹ Currently, ten community pharmacies are being piloted in Wales where they receive a summary of the DAL electronically, however this is limited to information about patients' medication. The aim of this study was to quantify the opinions of the public of Wales on community pharmacists having access to patients' full hospital DALs.

Approval was granted by the Cardiff School of Pharmacy and Pharmaceutical Sciences Ethics Committee. A questionnaire was designed previously by an MPharm student and 4000 questionnaires were distributed (with covering letter and freepost envelope) across Wales to a purposive sample of residents in five different local authorities.

This dissertation focuses on Cardiff where a 10.3% (n=134) response rate was achieved. Although results cannot be generalised due to the low response rate, majority of respondents agreed to share information including their time spent at hospital and other clinical and personal information with their community pharmacists providing information was kept confidential. Many respondents felt that verbal consent alone was not enough and that both verbal and written consent should be given.

With access to these full DALs, pharmacists could help improve overall patient care and safety. Findings from the full scale study will be passed on to NHS Wales Information Service to help them make a decision on whether the full hospital DAL can be accessed by community pharmacists.

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Synthesis of purine-based inhibitors of α B-crystallin as potential therapy against triple-negative breast cancer

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Triple-negative breast cancer (TNBC) has a particularly inferior prognosis and is the only immunohistochemistry subtype lacking targeted therapy.^{1,2} Protein-protein interaction (PPI) between alpha-B crystalline (CRYAB) and vascular endothelial growth factor (VEGF) has evolved as a promising target for TNBC. Targeting this pathway bears significant potential in suppressing tumour invasion and sensitising tumours to anti-cancer treatments without causing the side effects associated with affecting CRYAB expression.³ Through virtual screening, a purine-based lead compound was identified and optimised to give a target compound scaffold. The aim of this study was to prepare a series of target compound analogues for biological evaluation against TNBC cell lines. Other objective includes evaluating the compounds' potential in binding to CRYAB-VEGF interaction hotspot using molecular docking.

Synthesis of target compounds was first attempted through a four-step procedure starting from 4,5-diamino-2-mercaptopyrimidin-6-ol. It involved Traube synthesis, desulphurisation at position-2, dithiation at position-6 and 8, and subsequent alkylation at the 6-thio group. A second synthetic route consisted of three steps. The first two steps were achieved via alkylation of 6-mercaptapurine at the 6-thio group, followed by bromination at position-8. In both routes, purification was performed via recrystallisation and/or column chromatography and characterisation of products was achieved using NMR. Molecular docking was performed by docking the ligands into a pocket of human CRYAB crystal structure containing the hotspot.

The first synthetic route was unsuccessful. The second synthetic route successfully afforded a number of intermediates, which when undergoing nucleophilic substitution at position-8, would give a series of desired target compounds. Results from docking studies were encouraging, with three target compounds demonstrated better docking scores than the lead compound.

Upon successful completion of the synthesis of target compounds via the final plausible step provided, all target compounds will be tested against TNBC cell lines and the anticipated results will reveal their therapeutic potential.

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The impact of using the Welsh language in community pharmacy services: the pharmacists' views

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Communicating with patients in a way that they understand is a key skill for pharmacists.¹ Wales is a bilingual country and patients have the right to public services in Welsh. Welsh language initiatives have been put in place in order to strengthen Welsh language services in healthcare. Research involving patients' views on the Welsh language in pharmacy has provided evidence to show that being able to communicate in their first language does make a difference to them as they feel more at ease and are therefore more likely to open up about their healthcare and medication.²

Quantitative data was required for the study. Data was collected through the use of self-complete postal questionnaires. Questionnaires were sent to community pharmacies in areas with over 40% Welsh speakers: Carmarthenshire, Ceredigion, Gwynedd and Anglesey. The questionnaire was adapted from previous research investigating patient's views to now investigate pharmacists' views on the use of the Welsh language. Results show that pharmacists believe that language choice is important and makes a difference to patients but does not always affect the quality of care received. When referring to the Welsh language specifically results vary as the majority of Welsh speakers are fluent in English. Patients will not ask for their services in Welsh and Welsh speaking staff aren't well advertised. Attitudes towards Welsh language initiatives were positive.

Some pharmacists consider Language choice to be less important when referring to Welsh, however this conflicts with views of patients who feel that it still makes a difference as they are able to communicate more effectively in Welsh.³ The results highlight the importance of offering services in Welsh without patients having to ask or rely on prior knowledge as to whether or not staff can speak Welsh. Positive attitudes towards Welsh language initiatives could suggest high levels of participation in schemes.

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An analysis and evaluation of research regarding hospital patient medicines-related experience in Wales

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Patient satisfaction is used as an indicator of health service quality.¹ The measurement of patient satisfaction and experience in hospitals is essential to improve services and since reports have identified patient care as unsatisfactory² professional pharmacy standards have increased emphasis on patient-centred care and patient involvement in decisions about their care.^{3,4} This study collated results from a satisfaction survey conducted in Wales in autumn 2014 by previous MPharm students and compared the results to a similar study from spring 2014. A sample of pharmacists was interviewed to gather opinions on the provisional findings of the studies, information gathering from patients and how to improve transition of care.

Data collation and analysis was conducted within SPSS. Chi-squared, Kruskal-Wallis and Mann-Whitney U statistical tests were used to identify whether demographics or aspects of patients' hospital experience affected satisfaction. Interviews were transcribed and responses were categorised and analysed using a content theme analysis.

In the autumn 2014 study satisfaction was unaffected by demographics, day of discharge, Health Board or changes to medication. Satisfaction was higher in those taking fewer medications, who discussed medication with a doctor, who experienced no problems, who received verbal and written information and information about how their medication works and its potential problems. Overall satisfaction was over 80% in both 2014

studies and although results were similar, differences in the questionnaires used make them incomparable. Pharmacist interviews indicated that the best way to gather patient opinions is by a postal questionnaire (although it was highlighted that the questionnaires used could be enhanced). Transitional care between hospital and community pharmacies was believed to be poor.

Patient satisfaction in Wales is high and should be maintained. Further study with a redesigned questionnaire is recommended. Current transfer of information between care settings needs to be improved.

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Bacteriophage as a novel antimicrobial agent for dermal *Staphylococcus aureus* infections

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Bacteriophages can be used as antibiotic substitutes in the treatment of drug resistant bacteria. Bacteriophages have demonstrated efficacy in the treatment of *Staphylococcus aureus* infections in animal wounds¹ and clinical trials of patients with antibiotic resistance infections.² This study aims to determine the comparable efficacy of bacteriophages against antibiotics and skin disinfectants used in methicillin resistant *Staphylococcus aureus* (MRSA) decolonisation protocols.³ An *ex vivo* skin model⁴ was used to compare the bactericidal properties of a *Staphylococcus* bacteriophage, the antibiotic mupirocin and chlorhexidine digluconate skin cleanser.

A traditional streak assay was used to determine the efficacy of bacteriophage Card₁ against a range of *S. aureus* clinical isolates. The levels of bacteriophage mediated lysis against each strain was scored to determine the host range activity. An *ex vivo* assay using diffusion cells was used to determine the *ex-vivo* efficacy of the bacteriophage. Pig skin inoculated with *S. aureus* was treated with Card₁, mupirocin, or chlorhexidine digluconate for 24 hours. Surviving bacteria were enumerated to compare the reduction of viable bacteria between antimicrobial interventions.

Card₁ demonstrated broad spectrum activity against a range of *S. aureus* isolates. There was no significant difference in the reduction of bacteria between the bacteriophage Card₁, mupirocin, and chlorhexidine digluconate using the *ex-vivo* test.

The bacteriophage demonstrated equal efficacy to antimicrobials currently used in MRSA decolonisation protocols.³ Based on an *ex vivo* skin model,⁴ bacteriophage therapy has comparable bactericidal antimicrobial efficacy to conventional decolonisation agents in the treatment of *S. aureus* infections of the skin. Further optimisation of bacteriophage using multi-phage cocktails with wide host range activity would enhance bactericidal activity further. The implementation of bacteriophage therapy potentially widens the spectrum of antimicrobial agents alongside conventional decolonisation agents for resistant *S. aureus* infections.

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Investigating if patient training could influence the force people would use to apply a dummy microneedle patch

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First conceived in 1976,¹ microneedles are needles up to 1mm in length that are designed to breach the skin barrier. Microneedles overcome the drawbacks posed by conventional injections through painless delivery of drugs with a low risk of infection.²⁻⁴ Microneedle patches are being designed which require patients to manually apply a downward pressure to the patch to facilitate microneedle insertion into the skin. This study investigates whether patient training affects the forces used to apply a dummy microneedle patch and the short-term longevity of training effects.

50 subjects, aged 18-24 years old, were recruited through convenience sampling. Subjects were asked to apply what they perceived to be a suitable downward force to 'microneedle patches' to enable microneedle penetration (intuitive force). This force was recorded to either themselves or to another person, on both the forearm and deltoid. Subjects were then trained and asked to re-apply the force (trained force). Training consisted of counselling about microneedle application and the opportunity to practice application using a skin mimic. A questionnaire gathered the subjects' views towards the training. A follow up was carried out after 1-2 weeks to evaluate any changes in the application forces.

There was an overall reduction in the mean application forces and standard deviation after training, on both the forearm and deltoid (11.87±8.84N to 9.53±6.15N and 12.86±9.72N to 9.95±5.50N respectively). A feedback questionnaire revealed a positive response regarding the training and counselling.

Although there were positive indications, significant variability makes it difficult to conclude that training and counselling changes the application force used to apply microneedles in this small sub-group of the population. Despite subjects displaying a good attitude towards the training, further work is required to determine the potential benefit of training for the manual application of microneedles.

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Synthesis of 2'-fluoro ProTides as potential therapeutic agents and PET imaging probes

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Nucleoside analogues (NA) are extensively used antiviral and anticancer agents that have several limitations in their application. To overcome these, ProTides were designed to deliver the monophosphate form of the NA directly into the target cell using amino acid esters and aryl moieties to mask the negative charges.^{1,2} Since the failure of fialuridine (1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodouracil, or FIAU) in its phase II clinical trial,³ its corresponding radiolabeled compound has been used in reporter-gene imaging in Positron emission tomography (PET),⁴ but no further research has been carried out on it or its isomer 2'-deoxy-2'-fluoro-5-iodouridine. Therefore, the aim of this project is to firstly synthesise 2'-deoxy-2'-fluoro-5-iodouridine ProTides which will be evaluated for therapeutic activity and used as cold reference standards for the radiochemical synthesis of ¹⁸F-FIAU ProTides in the future and secondly, to start the synthesis of the ¹⁸F-FIAU ProTide precursor.

In the first part of the project, ProTide synthesis was based on phosphorochloridate chemistry via four major steps. It involved the reaction of L-alanine ester salts with phenyl dichlorophosphate to form the phosphorochloridates. These were further reacted with 2'-deoxy-2'-fluoro-5-iodouridine and NMI to form the ProTides. In the second part of the project, the initial step in the synthesis of ¹⁸F-FIAU ProTide precursor involved the reaction of 5-iodouridine with 1,3-dichloro-1,1,3,3-tetraisopropylidisiloxane (TIPDSiCl₂).

The methyl, ethyl and *tert*-butyl derivatives of the ProTides were obtained as mixtures of diastereoisomers at low yields. The isopropyl, neopentyl and benzyl phosphorochloridates have been synthesised and need to be coupled in the final step and lastly, the initial step in the synthesis of the precursor was successfully completed.

To conclude, the ProTide derivatives were successfully synthesised, purified and characterised but several other derivatives still need to be synthesised and in order to be analysed *in-vitro* for potential activity. Finally, the ^{18}F -FIAU ProTide precursor synthesis needs to be completed and radiolabeled for further development into a novel PET imaging probe in the future.

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An evaluation of inhaler technique in patients of the Cardiff and Vale Health Board

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Inhaled medications are effective in treating respiratory conditions; they provide local delivery, a fast onset of action and a reduction in side effects.¹ In order to receive a sufficient dose inhaler technique needs to be correct. Poor inhaler technique is a common barrier resulting in reduced therapeutic benefit and compromised disease control.²

This study aimed to evaluate how effective inhaler technique is in the patient population and investigate for factors that may influence this. Participants were recruited from primary and secondary care sites. Information about inhaler use, training and knowledge was obtained. A test of inhaler technique was performed using a Vitalograph Aerosol Inhalation Monitor (AIM) device. This measured: inspiratory acceleration, timing of activation, inspiratory flow rate, inhalation time and breath hold time.³ Data was analysed using Chi-squared with $P < 0.05$ accepted as statistically significant.

Poor inhaler technique was observed in 59% of the participants. Significantly, more patients using a pMDI failed the inhaler test (83%) than those using the pMDI with a spacer (9%) or a DPI (17%). Older patients demonstrated significantly worse inhaler technique with pMDIs. Receiving device training from a health care professional made no impact on how well participants could use their inhaler. Most patients had been trained by a nurse, only one patient was shown by a pharmacist.

Incorrect technique with a pMDI alone is common however; technique with a spacer is better suggesting spacers can help. Results demonstrate that the training given is ineffective at providing patients with the ability to use inhalers correctly. To combat this, health care professionals may need better training too.⁴ Community pharmacists need to be more engaged in providing inhaler technique training; they are conveniently located for patients and have the expert knowledge for them to do so successfully.

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Paliperidone long-acting injection: one-year outcomes in a retrospective naturalistic follow up study

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Paliperidone long-acting injection (PLAI) is licensed for maintenance of schizophrenia and schizoaffective disorder in patients who were previously responsive to risperidone or paliperidone.¹ There are a limited number of studies available that assess the efficacy of PLAI which are reflective of the patients seen in practice.^{2,3} The main aim of this naturalistic study was to assess the effectiveness of PLAI using outcomes relevant to clinical treatment. The outcome measures used to determine effectiveness were treatment continuation at one year, and for continuers, inpatient stay prior to and following treatment initiation.

A retrospective case note review was conducted at Whitchurch Hospital including patients who had received PLAI prior to 1st December 2014 in the Cardiff and Vale area. Patients were categorised as either continuers or discontinuers. Demographic factors which may have influenced outcomes were analysed. Secondary outcomes for discontinuers included subsequent treatment strategy, final dose of PLAI and reason for treatment discontinuation.

In total, 62 patients were identified as receiving PLAI and 65% of them were continuers at one year. The most common reason for discontinuation was lack of effect (41% of discontinuers). Out of all patients, 15% discontinued due to side effects. A mirror image comparison disclosed no statistically significant reduction in the number of inpatient days prior to and post PLAI initiation. Age on initiation of discontinuers were younger than continuers ($p=0.0178$). The use of oral risperidone prior to PLAI led to a higher likelihood of discontinuation within the unlicensed users ($p=0.0242$), but there were only 11 patients within this group.

Factors that determined discontinuation in this study were a younger age on initiation and previous treatment, within unlicensed use. A larger patient cohort and a longer study period are needed to further evaluate the long term effectiveness of this drug.

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Identifying and exploring factors affecting student motivation for the MPharm: a qualitative study

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Motivation has been defined as what 'moves you to do something'.¹ The distinction between intrinsic and extrinsic motivational factors has been important in the development of various educational practices, particularly as a student's performance is affected by their motivation for studying and their ability to attain knowledge. Students displaying intrinsic motivation perform activities because of inherent interest whereas extrinsically motivated students perform activities to achieve a desirable outcome.² As limited research has been conducted in the context of pharmacy, the aim of this study is to investigate factors that affect the motivation of final year MPharm students.

Students were selected by non-probability (purposive and convenience) sampling to achieve a broad demographic. After conducting a literature review the research team developed a topic guide. After gaining ethics approval and participant consent, 24 one-to-one semi structured interviews were conducted and audio recorded by the research team. Qualitative data was transcribed 'ad verbatim' and analysed primarily using inductive thematic analysis,³ deductive reasoning and Deci and Ryan's self determination theory [1] where appropriate.

Five main themes were identified from the data set: assessments, influence of others, interest in subject, competing interests and session attendance. There were several key motivating factors for final year students.

Most were extrinsically motivated towards higher weighted assessments. Changes in motivation through the degree were also reported. They were also intrinsically motivated towards assessments they found interesting and enjoyable. The participants also mentioned demotivational factors; these could be addressed by Cardiff School of Pharmacy and Pharmaceutical Sciences (CSPPS) to help improve overall student motivation.

This study has shown that student motivation is individualistic and multifactorial. The results have identified factors that have both positive and negative effects on student motivation with students also suggesting methods that CSPPS can adopt to increase motivation. As student motivation changes throughout the MPharm degree, further longitudinal studies are required.

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Non-medical prescribing: models in pharmacy

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Non-medical prescribing is defined as prescribing undertaken by a healthcare professional who is not a doctor.¹ It began with the Cumberlege report in 1986 followed by the Crown Reports in 1989 and 1999 which led to the introduction of supplementary prescribing and independent prescribing.² There is limited research into pharmacy prescribing models therefore the aim of this project is to explore these models in both primary and secondary care.

Ethical approval was granted by the Cardiff School of Pharmacy and Pharmaceutical Sciences' school Ethics committee. Qualitative methodology was deemed most appropriate and semi-structured interviews were used to collect data. Purposive and convenience sampling methods were used and the interview schedule was adapted from that of the previous project, which this was a continuation of. Recruitment was by advertisements and the interviews were analysed using thematic analysis.

The main facilitators identified included positive working relationships and support. Identified barriers included lack of support and role recognition, concerns about assessment skills and funding and the results also demonstrated a need for promotion of the role. The main driver for pharmacists to prescribe and their advantages and disadvantages of prescribing were also highlighted. Case studies for models of practice were successfully developed to highlight how and where pharmacists were prescribing.

This research explored the views and experiences of prescribing pharmacists and several key facilitators and barriers have been identified. It has established key areas of support which are needed and highlighted the need for promoting the role more effectively. All of the above should be shared within the profession to help it to develop and expand. Additionally, it would be appropriate to explore this area further with a larger number of participants by conducting a survey of all registered pharmacist prescribers.

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A comparison of the puncture properties of two types of hypromellose capsules

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Simple single-unit dosage systems such as two-piece hard capsules in dry powder inhalers (DPIs) are widely used for pulmonary drug delivery.¹ Hypromellose capsules have shown superior puncture properties over gelatin capsules in previous studies.² Hypromellose capsules chosen for their mechanical properties, Quali-V-I® capsules, are currently used in single-unit DPI devices. There is another commercially available hypromellose capsule of a different grade, used for oral drug delivery, Quali-V® capsules.³ The aim of this

study is to compare puncture properties of Quali-V-I® and Quali-V® capsules within their approved moisture specifications.

Capsules were conditioned in desiccators containing saturated salt solutions controlling the relative humidity (RH) adjusting moisture content to each end of the moisture specification. Both types of capsules were stored in a desiccator containing either CaCl_2 (33% RH) to reduce the moisture content or $\text{Mg}(\text{NO}_3)_2$ (56% RH) to increase moisture content. Capsule samples ($n=10$) of Quali-V® and Quali-V-I® taken from the desiccators were placed in a Zwick® materials testing machine. Force taken to puncture each capsule using a conical-tipped pin was recorded. Puncture holes created in the capsules were photographed using light microscopy with an integrated camera. Puncture holes were assessed for size, circularity and flap attachment for comparison between the capsule samples.

Conditioned capsule samples fell within the moisture specification lower end but slightly above at the upper end. Further studies are required to compare puncture properties within their moisture content specification. Quali-V-I® capsule samples required increased puncture forces compared to Quali-V® capsules. Quali-V-I® capsules' puncture hole characteristics were superior, with increased area and circularity. Puncture force required was greater in capsule samples of lower moisture content, however the resulting puncture hole was more uniform with increased area.

Overall, Quali-V-I® capsules required increased puncture force but showed superiority in the resulting capsule puncture compared to Quali-V® capsules.

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Investigating the role of ZIP7 phosphorylation in breast cancer

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Zinc is a crucial trace element with a key role in regulation of normal cell growth and proliferation.¹ The homeostasis of zinc relies heavily on transporters to move zinc in and out of the cytoplasm, these transporters including ZIP and ZnT channels.² ZIP7 is a transporter moving zinc into the cytoplasm; this zinc release drives downstream effects and cell proliferation.³ Tamoxifen resistant breast cancer cells overexpress ZIP7 compared to normal cells, suggesting a role in driving breast cancer.⁴ The aim of this study was to discover if there was any difference between two residues on ZIP7, S275 and S276, in their role in ZIP7 activation and subsequent downstream effects.

Western blotting was used to detect proteins of interest from cell samples. Cells were transfected with ZIP7 mutants, before treatment with zinc and sample collection at various time points. The mutants used were S275D/S276A, S275A/S276D and S275A/S276A. Desirable proteins were probed for using specific antibodies and detected via chemiluminescence. Densitometry was used to quantitatively analyse the proteins presence in the sample.

Results for both the pZIP7 and one of the main downstream effector proteins, pAKT, agreed with previous data. pAKT was activated in response to ZIP7 activation which explains its role in driving cell growth and proliferation. GSK-3Beta appears to be directly inhibited by zinc and pAKT has less impact on this effector protein. Both residues S275 and S276 appear necessary for ZIP7 activation. A lack of pZIP7 and decreased pAKT occurred in the samples with a removed phosphorylation site.

The importance of both residues for activation suggests antagonism at one residue may be enough to inhibit ZIP7 activation. Further research is needed to statistically back up the evidence and to further explore the plausibility of ZIP7 as a therapeutic target in anti-endocrine resistant breast cancer.

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A service evaluation on the use of an electronic portal to assess patient measures in a Parkinson's disease clinic

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For patients with Parkinson's disease, non-motor symptoms, such as depression, urinary incontinence and dizziness have been found to be the largest contributor to quality of life.¹ Such symptoms are currently identified by completion of a non-motor symptom paper questionnaire.² It has been recognised that an electronic portal, such as an iPad application, encompassing the non-motor symptom questionnaire may aid the monitoring of such symptoms. The majority of Parkinson's patients are elderly, most being over 50 years old,³ with many individuals suffering from dyskinesia and tremor.¹ This raises concerns over the usability of an iPad application. The main aim of this study was to evaluate the feasibility of using an iPad application within a Parkinson's disease clinic.

A service evaluation was carried out to gain understanding of how patients and staff felt about the use of an electronic portal within their clinic. Interview questions were formulated, comprising of both closed and open-ended questions. Patients were invited to use the iPad application and subsequently partake in an interview. Staff members were also asked to partake in interviews.

Of the patients who were interviewed (N=24) it was found that although 54% of patients (N=13) had never used an iPad before, 88% of patients (N=21) felt comfortable using the application provided. All staff members interviewed (N=5) felt that patients would need assistance to use the iPads and provisions need to be made for this.

Throughout the course of the service evaluation, potential issues were identified, such as staff concerns regarding time constraints within clinic and patient concerns over usability of the application. All of which can be addressed with simple changes as recommended. The results from this service evaluation have proven useful and with the recommendations made the service shows promise in being introduced in the near future.

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How does patient training affect the application forces that people use to apply microneedle patches?

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First proposed in 1976,¹ microneedles (MNs) can deliver drugs across the skin without causing pain or bleeding² and have minimal infection risk. The use of MNs by patients is less understood, with two previous studies demonstrating successful application following instructions.^{3,4} A previously unpublished study indicates a wide variability (2-60N) in the intuitive forces people use to apply "dummy" MNs, which may lead to inconsistent amounts of drug delivered. Our study aims to determine the impact of training on the forces volunteers use to apply "dummy" MNs, and the short-term longevity of any training effect.

Volunteers (n=50; aged 18-25) applied intuitive forces with a digital pressure gauge on "dummy" MN patches on the forearm and deltoid. Training comprised verbal instruction and practice applications on a skin mimic. Volunteers then applied force again after training. A feedback questionnaire was administered to gather volunteers' views on the training. After 7-14 days, the same volunteers made another application without any re-training given.

Training reduced the magnitude and standard deviation of forces for both application sites, with the deltoid showing a statistically significant reduction (12.86±9.72N to 9.95±5.50N). After 7-14 days, there was a small increase in the magnitude and standard deviation of application forces for both sites, but it was not statistically significant. Responses from the feedback questionnaire indicated that 78% volunteers had increased confidence in the suitability of the application force they used after training.

This study indicates that training can reduce the variability of the application forces used, thus enhancing usability of potential MN products. Improvements to the skin mimic is needed for future studies. Training is still effective after 7-14 days, suggesting that it has some longevity and re-training for patients in future clinical settings may not be needed, saving time and cost.

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Determination of skin biomechanical properties on human volunteers

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Microneedles (MNs) exploit the advantages of transdermal drug delivery route.^{1,2} One approach to use the MNs is to coat the drug onto individual MN surfaces and insert them into the skin. There are several relevant parameters that could possibly affect MN delivery such as skin biomechanical properties, degree of skin hydration and possibly skin temperature. Skin is elastic therefore ensuring MN penetration is challenging. Thus, this study involves looking into these parameters in human volunteers and understanding more about biomechanical properties of skin, hydration and temperature at two different application sites, the palms and forearms. We then compare the human volunteer data with an *ex vivo* human skin model that is currently used as a laboratory surrogate for *in vivo* human skin to confirm comparable skin biomechanics.

An indentation technique was used to measure skin displacement as a function of force.^{3,4} Skin hydration was measured as transepidermal water loss (TEWL) and temperature of the skin was also measured. In order to create hydrated skin, the forearm was occluded with cling film for 3 hours. Elevated TEWL values were measured after occlusion.

Results demonstrated that biomechanical properties of skin differ significantly at different body regions. Regional variation was also observed on hydration state of skin. An occlusion effect was determined as TEWL values were significantly increased after application of cling film. The adapted *ex vivo* skin model in this study is currently not representative of *in vivo* skin from a biomechanical perspective.

In conclusion, this study provided meaningful information on skin mechanical behaviour, which can be used to optimise the *ex vivo* skin model for future MN testing. Relevant parameters such as biomechanical properties of skin, skin hydration and skin temperature should be taken into consideration when measuring MN performance.

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Synthesis of CYP24A1 Inhibitors as Potential Cancer Therapeutics

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Calcitriol ($1\alpha,25\text{-(OH)}_2\text{D}_3$), the most potent metabolite of Vitamin D has been proven to have an anti-proliferative and anti-inflammatory effect against malignant cells in cancer therapy.¹ Studies have shown that increased calcitriol levels decrease the risk of prostate cancer, colon cancer¹ and breast cancer.² However, calcitriol treatment is limited by the up-regulation of the CYP24A1 enzyme, which is responsible for catabolism of calcitriol.³ Hence, this research aimed to identify and synthesise new, potent and selective CYP24A1

inhibitors which will decrease the catabolism of calcitriol, extend calcitriol half-life, and increase the calcitriol exposure for cancer therapy.

In this research, molecular modelling using MOE was done to visualise the possibility of interactions between the target compounds with the homology model of CYP24A1⁴ and identify compounds with potential CYP24A1 inhibitory effect. Then a three-step synthesis which involved formation of amide; then cyclisation to oxazole and lastly nucleophilic ring opening to imidazole, was performed in the laboratory. All the end products in each step of the synthesis were analysed using TLC, NMR, and then microanalysis to check on the purity of the compounds.

All the products were successfully synthesised with good yield except for the final compounds, which have low yield. Considerable amounts of the product were lost during the trial and error of finding a suitable solvent for recrystallisation. Nevertheless, high purity compounds were obtained at the end of the project according to the NMR and microanalysis results.

Since the results from molecular docking showed theoretically promising outcomes, biological evaluation should be done to determine activity. If any inhibitory activity were shown in the compound, structure-activity relationship analysis by modifying the chemical structure should be performed.

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The following abstracts have been withheld as they have been or will be published elsewhere, and/or due to intellectual property or confidentiality issues:

Analysis of the physico-chemical properties of peptide cargo delivered into cells by cell penetrating peptides

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Analysis of the peptide EJP18 as a potential Epidermal Growth Factor Receptor (EGFR) targeting bioportide

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Developing methods for characterising cell penetrating-peptide non-covalent complexes

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Co-formulated chloramphenicol and sodium fusidate for treating acute bacterial conjunctivitis

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Do oral HMG-CoA reductase inhibitors (statins) reduce the incidence of surgical site infections (SSI'S) in patients, who have undergone an elective primary hip or knee arthroplasty procedure?

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Hip and knee replacement surgery is the most prevalent and successful type of surgical intervention that is performed on both the majority of the elderly and some young NHS and private patients who have experienced the debilitating symptoms of osteoarthritis (OA).

The majority of OA patients find that the clinical symptoms of OA are only alleviated after they have had primary hip or knee arthroplasty. However even though a total hip or knee arthroplasty is normally a safe and effective surgical procedure, this type of surgery carries the risk of patients developing post-operative surgical site infections (SSI).

Surgical site infections (SSI) can be very difficult to treat and there have not been many potential preventative treatment options available until fairly recently. A potential treatment option involves the use of HMG-CoA reductase inhibitors which are more commonly known as statins.

This retrospective clinical trial used the Royal Orthopaedic Hospital, Birmingham's surgical site infection database which contained 202 surgically infected primary hip and knee patients and matched them with 202 non-surgically infected primary hip and knee patients from the Royal Orthopaedic Hospital Birmingham's health informatics hip and knee database using specific risk factors and propensity score matching to analyse if there was a difference in statin use.

The results from the clinical trial demonstrated that the non-SSI hip and knee cohort were less likely to develop a surgical site infection because they were on statin treatment (95% confidence interval, $P < 0.0001$) and that of those in the SSI and non-SSI hip and knee cohort that did take a statin (52 patients and 68 patients) 58% in the SSI knee and hip cohort and 75% in the non-SSI knee and hip cohort took simvastatin at night. This indicates that statin use was associated with a reduced incidence in the development of a surgical site infection in those patients who had undergone an elective primary hip or knee arthroplasty procedure.

SK Potassium and TRPM7 ion channel role in CNS cell survival and breast cancer cell death decisions

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Cell survival is modulated by a cocktail of ion channels engaging cell life and death decisions through controlling key cellular messages such as apoptosis and proliferation. Unnatural regulation of these processes results in various disorders, for example neurodegenerative diseases, as well as the cancers. Nowadays, these pathologies are affecting millions of people per year in the world. Potassium (K^+) ion channels appear to play a potent role in such illnesses since they control many cellular gates in cell physiology such as ionic homeostasis and signalling cascades. Amongst the K^+ channels, small (SK1-3) and intermediate (SK4) conductance Ca^{2+} -activated potassium ion channels have recently been shown to save cells, thereby protecting mitochondrial function which serves as a cell survival platform. In the case of other ion channels, for instance transient receptor potential melastatin 7 (TRPM7), it is also repeatedly stated that such membrane channels shows an impressive and differential role in excitable and non-excitable cell survival. This channel also modulates ionic homeostasis of crucial species in cellular physiology such as Ca^{2+} . This study reveals that central nervous system (CNS) and breast cancer cells differentially express SK1-4 ion channel subtypes, and their functional presence is pharmacologically confirmed, however, in most cases these results were further clarified through small interference RNA (siRNA) methods. Similarly, functional TRPM7 channel expression in CNS cells is also confirmed. In the CNS, SK1-4 channel activation rescues neurons from oxidative stress, whereas, TRPM7 channel inhibition protects CNS cells from a hydrogen peroxide (H_2O_2) harmful effect, as well as hypoxia and apoptosis, so improving cell survival. Excitingly, SK1-4 channels differentially exist in wild-type and Huntington's affected mouse striatal cells, where diseased cells lack SK1-3 channels, key players in action potential activity. Interestingly, SK2 or SK3 channel subtypes are also functionally expressed in breast cancer cells with various phenotypes. This study established that these ion channels are powerful agents in a survival role, in fact controlling growth through cross-talk with an apoptotic avenue "intrinsic pathway". SK2 or SK3 channel activation enhances cell viability, while its inhibition dampens cell growth. It is very noteworthy that SK2 and SK3 channels are not expressed in non-tumorigenic breast cells.

In brief, SK1-4 and TRPM7 molecules are clearly implicated in the survival of diverse cell types through an apoptotic route, indicating that these ionic regulators are promising targets in channelopathies related to cellular degeneration and growth.

The exploration of CD44 as a mediator of a drug resistant phenotype in ER+ breast cancer

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The majority of breast cancers express the oestrogen receptor and are potentially amenable to endocrine therapy, however the clinical effectiveness of these agents is limited by the phenomenon of acquired resistance which is associated with disease relapse and poor prognosis. It has been previously demonstrated that the CD44 receptor is overexpressed in acquired tamoxifen resistance where it associates with an enhanced migratory phenotype, however little is known regarding the effects of CD44 splice variants in this context. This thesis aimed to explore the role of CD44 variant isoforms in a model of ER+ breast cancer derived tamoxifen-resistance (TamR cells) and expand these explorations into an additional model of acquired fulvestrant-resistance (Fas-R cells).

Multiple CD44 isoforms were found to be upregulated in resistance although a differential expression profile was observed between Tam-R and Fas-R cells. Inhibition of global CD44 expression in both endocrine resistant models led to a loss in their migratory, proliferative and invasive capacity and attenuated their responses to the CD44 ligand, hyaluronan. Overexpression of CD44v6 in endocrine sensitive MCF-7 cells induced EGFR pathway activation leading to enhanced cellular invasion, and attenuated response to fulvestrant. Accordingly, CD44v6 suppression in Tam-R cells resulted in a loss of EGFR pathway signalling and reduced invasion. Preliminary clinical analysis revealed that co-expression of CD44v6 and EGFR associated with a trend for worsened outcome in ER+ breast cancer patients treated with tamoxifen.

These data suggest that upregulation of CD44v6 may contribute to an aggressive phenotype in tamoxifen resistant cells through a mechanism involving the EGFR. Future use of CD44v6 and EGFR as biomarkers may have potential therapeutic value to predict a cohort of ER+ breast cancer patients which relapse earlier on tamoxifen and may thus require more aggressive treatment strategies.

The antibacterial activity of *Humulus lupulus* against mycobacteria

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One third of the world's population is estimated to be infected with *M. tuberculosis*, a pathogen which causes more human death and misery than any other bacterial disease. Whilst treatment is available, resistance to commonly used antimicrobials is a growing problem. Thus there is an urgent need to identify new compounds that can kill drug resistant isolates and are able to potentiate the activity of currently available antibiotics.

The plant kingdom is a rich source of antibacterial compounds and a plant which has attracted particular interest is *Humulus lupulus*, more commonly known as the hop, which has been used as an antibacterial in beer for hundreds of years. Its antibacterial properties are thought to be due to the combined action of alpha and beta acids and polyphenols such as xanthohumol although the precise nature of their interactions and relative importance has yet to be determined.

An optimized agar antimicrobial assay was developed and employed based on *Mycobacterium smegmatis*, to characterize the antibacterial activity of fifty commercially available hop varieties with a view to identifying novel antibacterial compounds. Surprisingly, no correlation was found between alpha and beta acid content and antibacterial activity. Chemical analysis of the most (Citra) and least (Galena) active hop variants using a combination of bioactivity based thin layer chromatography, mass spectrometry and HPLC revealed differences in the relative amounts of antimicrobial compounds such as humulone (alpha acid), lupulone (beta acid) and xanthohumol but failed to identify the presence of novel antibacterial compounds.

Whilst no new antimicrobial compounds were identified, the Citra hop extract was able to potentiate the activity of the antibiotics imipenem and ciprofloxacin against clinical isolates of *M. abscessus*, a fast growing member of the mycobacterium family which infects individuals suffering from cystic fibrosis. The Citra hop extract also inhibited the growth drug resistant isolates of *M. abscessus* suggesting that it may have activity against other antibiotic resistant mycobacteria such as *M. tuberculosis*.

With regards to the mode of action, scanning electron microscopy revealed distinct changes to the outer cell structure of the bacteria, suggesting that hops contain compounds that interact with the bacterial cell membrane and/or cell wall.

These changes were more profound in the presence of sub-inhibitory concentrations of imipenem, a compound which also targets the cell wall. Overall hops were shown to contain compounds which inhibited the growth of mycobacterium and were able to potentiate the activity of antibiotics currently used to treat these pathogens. These findings suggest hops may be a fruitful source from which to isolate next generation compounds with which to treat increasingly drug resistant strains of mycobacteria.

Investigating antibacterial plant-derived compounds from natural honey

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Honey possesses therapeutic properties which are the result of a range of factors including high sugar content, low pH, hydrogen peroxide and bee-derived peptides. Honey also contains antimicrobial phytochemicals which represent a rich source of leads for the development of drugs for the treatment of microbial infections.

Honey samples donated by UK beekeepers (217) and Manuka samples (3) were screened for the presence of novel antibacterial compounds by determining activity against methicillin resistant *Staphylococcus aureus* (MRSA) using optimized agar well diffusion and broth micro-dilution assays. The majority (92%) of the honeys showed inhibitory activity. Identification of unknown factors was performed by neutralizing antibacterial honey

components previously described in the literature. Of the samples screened four samples were found to contain potentially novel antibacterial compounds.

The pollen present in honey represents a record of the plants which contributed to the making of the honey and may be the source of specific antibacterial factors. For this reason pollen was extracted from honey samples which demonstrated high levels of antimicrobial activity. Microscopic and DNA meta-barcoding (454 and Illumina) analysis was performed. Plant species identified with DNA meta-barcoding provided superior discrimination and greater repeatability. Key species identified in the antibacterial samples included woodruff (*Galium odoratum*), bluebell (*Hyacinthoides non-scripta*) and dandelion (*Taraxacum officinale*).

Extracts from active honeys and characterised plants demonstrated antibacterial activity against MRSA, *E. coli* and *P. aeruginosa* using broth based methods and thin layer chromatography (TLC) bio-autographic overlay methods. Activity-guided characterization using a TLC/mass spectrometry (MS) interface and high performance liquid chromatography (HPLC) was performed. Compounds identified using these approaches included known pinobanksin derivatives and unknown compounds suggesting that the plants may be the original source of active compounds. The demonstration of antibacterial activity may provide new lead compounds that could serve as selective agents against MRSA and other antibiotic resistant bacteria.

Focal Adhesion Kinase (FAK) as a novel therapeutic target in HER2+ breast cancer

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Focal Adhesion Kinase (FAK) is an intracellular kinase known to mediate integrin signalling following cell adhesion to the extracellular matrix. It is now emerging as a promising therapeutic target in many tumour types due to its overexpression in tumour cells and is associated with various cellular processes involved in cancer progression. Given that existing literature demonstrating that FAK plays a key role in the transduction of HER2 signalling in HER2+ cells and that the levels of FAK expression strongly correlated with HER2 overexpression in clinical samples, we explored the potential for improvement of current therapies for HER2+ breast cancer by combination treatment strategies with the small molecule FAK inhibitor, PF878.

FAK activity was assessed in a panel of cell lines reflecting HER2- (MCF7, T47D) and HER2+ (BT474, MDA-361, SKBr3) disease by Western blotting. FAK activity was relatively increased in HER2+ versus HER2- cell lines with HER2+ cells demonstrating greatest sensitivity to PF878 with respect to suppression of FAK phosphorylation at Y397. The effects of PF878 on cell proliferation as a monotherapy and in combination with Herceptin were assessed using MTT and direct coulter cell counting and by Ki67 immuno-staining. Whilst PF878 did not affect the proliferation as a monotherapy, treatment of HER2+ cells with PF878 and Herceptin combined resulted in synergistic inhibitory action on cell proliferation with an associated suppression in AKT pathway activity. This combination treatment strategy produced the greatest effects in MDA-361 cells which were intrinsically insensitive to Herceptin-monotherapy.

Inhibition of FAK activity also suppressed HER2+ cell migration in response to the exogenous ligand Heregulin and to conditioned-media derived from fibroblasts as assessed in Boyden Chamber migration assays. In this latter context, our data suggests that FAK may act through a STAT3-dependent mechanism to regulate fibroblast-stimulated migratory and invasive responses. Collectively, these data support a role for FAK in HER2+ breast cancer where its targeting has the potential to improve Herceptin response as well as suppress stromal-induced signalling that can contribute to disease progression and spread.

Interfacial phenomena between bacterial or mammalian cells and orthopaedic biomaterials

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Adhesion as a scientific phenomenon has been researched for the past 70 years, as the notion of two entities contacting effects a huge expanse of daily activities, from writing to sophisticated cellular and bacterial interactions essential for growth and survival.

Inherently, a robust and adequate model of adhesion was acquired, one in which biological aspects were considered. Initially, the methodology required was optimised using the atomic force microscope (AFM) by testing a model bone substrate against ultra-high molecular weight polyethylene (UHMWPE), a material commonly found in the articulating acetabular cup. Once a force mapping technique was established experimentation continued to bacterial adhesion against model bone samples of various roughness, establishing that the adhesion phenomena occurs at a scale dependency due to the alterations in the topography of the surface at the micro to nano level.

Aseptic loosening and osteolysis are major causes of failures in implanted biomedical devices at the hip. These issues are governed by the deterioration of the moving components, producing particles known as wear debris associated with the metals, bone cement, and UHMWPE materials initiating an immune response which is detrimental to the surrounding cells and tissues adjacent to the implant. The notion of mechanical aspects altering the health of mammalian cells has been ignored throughout the research of implantations and their effect on the cells by foreign bodies; the only concept studied to date is the viability and functionality post exposure. Therefore, this thesis aims at observing ii mesenchymal and osteoblast (both rodent and human) cells associated to wear debris (metal and polymeric particles of various sizes and compositions) exposure and the effect this has on cell nanomechanical and adhesive properties using the AFM techniques. The data obtained indicated that Cobalt nanoparticles were more damaging on all cell types than Titanium and polymeric particles.

Investigation into the effects of zinc on the anti-breast cancer properties of disulfiram

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Breast cancer is the second-leading cause of cancer related death in women and future therapies may involve the strategic use of previously developed drugs, which have established toxicity profiles and are often ex-patent. The alcohol-deterrent disulfiram has been proposed as an anti-cancer agent, based on its capacity to interact with copper-dependent processes. However, little has been done to determine the relationship between this drug and zinc, despite knowledge that disulfiram binds this metal and zinc levels are dysregulated in breast cancer. This thesis investigated whether zinc is an important factor when considering disulfiram efficacy as an anti-breast cancer agent.

Disulfiram was toxic to MCF-7 and BT474 breast cancer cell lines and produced a striking time-dependent biphasic toxicity response between 5- 20 μ M. Co-incubation of the drug with low-level zinc removed this effect, suggesting that the availability of extracellular zinc significantly influenced disulfiram efficacy. Structure-activity relationship studies with disulfiram analogues revealed the biphasic effect could be influenced by altering the size of chemical groups bound to the drug's nitrogen atom.

Live-cell confocal microscopy using fluorescent endocytic probes and the zinc dye FluoZin-3, coupled with the development of a complimentary FluoZin-3 flow cytometry assay found that disulfiram rapidly increased zinc levels in breast cancer cells specifically in endo-lysosomes. This indicates that the ii cytotoxic effects of this drug may be due to acute zinc overload. Further investigation into disulfiram effects on lysosomes suggested that the drug disrupts lysosomal membranes and releases hydrolytic enzymes into the cytosol. Lysosomal membrane permeabilisation has been demonstrated to promote apoptosis and may be a mechanism to explain disulfiram cytotoxicity in breast cancer. This could have important clinical implications in situations of high intracellular zinc as seen in breast tumours, indicating that breast cancer cells may be more susceptible to the zinc ionophore action of disulfiram than non-cancer cells.

The role of BCA2 in receptor tyrosine kinase endocytosis and breast cancer

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Breast Cancer Associated gene 2 (BCA2), is a little-studied E3 ligase that is overexpressed in 56% of all primary breast cancers and has been linked with increased cell proliferation and invasion in vitro. BCA2 has been implicated in EGFR degradation however there is conflicting evidence surrounding its function and effect

on receptor biology. This project aimed to elucidate the role of BCA2 in EGFR endocytosis and downregulation and to determine its link with breast cancer survival.

Data generated with online mRNA analysis tools indicated that high BCA2 levels were often associated with improved breast cancer prognosis. In silico studies also demonstrated that many genes coexpressed with BCA2 were regulators of membrane trafficking and suggested that BCA2 expression was repressed by HER2/EGFR/Ras signalling.

Experimentally, it was shown that siRNA depletion of BCA2 led to increased EGFR protein levels while transient BCA2 overexpression reduced levels of the receptor. It was found that BCA2 overexpressing, EGF stimulated cells demonstrated reduced lysosomal degradation of both receptor and ligand. Associated with this, downstream EGFR signalling in BCA2 overexpressing cells was reduced in magnitude but prolonged in duration and ultimately cell viability was impaired.

These findings support a role for BCA2 in the endolysosomal system. In agreement with this it was shown that BCA2 overexpression inhibited the vesicle membrane association of Rab7, a regulator of late endocytosis and reported BCA2 interactor. Transferrin receptor levels and transferrin uptake were unaffected by BCA2 overexpression suggesting trafficking effects may be restricted to EGFR, a distinct class of receptor and/or to later (degradation) stages of endocytosis.

This thesis provides a detailed exploration of BCA2 biology and presents evidence of a functional role for the protein in the endocytic regulation of EGFR. The mechanism/s underlying the complex relationship between BCA2 and breast cancer outcome have yet to be fully determined.

Peptide-coated microneedles for antigen specific immunotherapy of type 1 diabetes

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Type 1 diabetes is an autoimmune disorder caused by the destruction of insulin secreting β cells in the pancreas. The aim of this project is to explore the potential of using solid-coated microneedles to target skin dendritic cells with an auto-antigen to induce tolerance for the treatment of type 1 diabetes.

A novel coating formulation has been developed to accommodate peptides with different lipophilicities. The optimised coating formulation and electro-polishing of the microneedle surface were key factors which enhance the efficiency of peptide delivery. Optimised coating formulation did not show adverse effects on peptide bioactivity or trigger a pro-inflammatory response.

The delivery route (microneedle vs. intradermal injection) was shown to be the main factor that influenced the clearance of peptide from murine skin in vivo. Other factors such as temperature, skin hydration state and peptide solubility were also shown to have effects on peptide clearance.

Two autoantigens were used to induce tolerance in non-obese diabetic mice – a potent mimotope m31 and endogenous antigen WE14. The proliferation profile of transferred carboxyfluorescein succinimidyl ester labelled BDC2.5 T cells in pancreatic lymph nodes in non-obese diabetic mice was used as a readout for the development of immunological tolerance. The results herein provide the first demonstration that WE14-coated microneedles were able to induce tolerance in vivo, showing reduced proliferation of BDC2.5 T cells.

Additionally, this project examined the potential of short-term topical application of betamethasone to enhance peptide-induced tolerance. Both human and mouse dendritic cells showed a pro-tolerogenic state after treatment with topical application of betamethasone in vitro. However, full dose betamethasone was shown to have systemic toxicity in vivo, resulting in depletion of CD11c+ dendritic cells and CD4+ T cells. Diluted topical betamethasone facilitated a small effect on BDC2.5 proliferation; however no advantage on enhancing antigen specific immunotherapy was observed.

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